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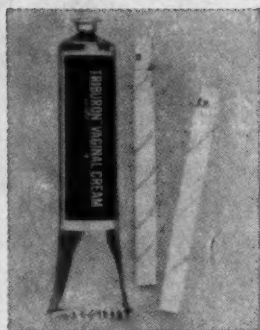
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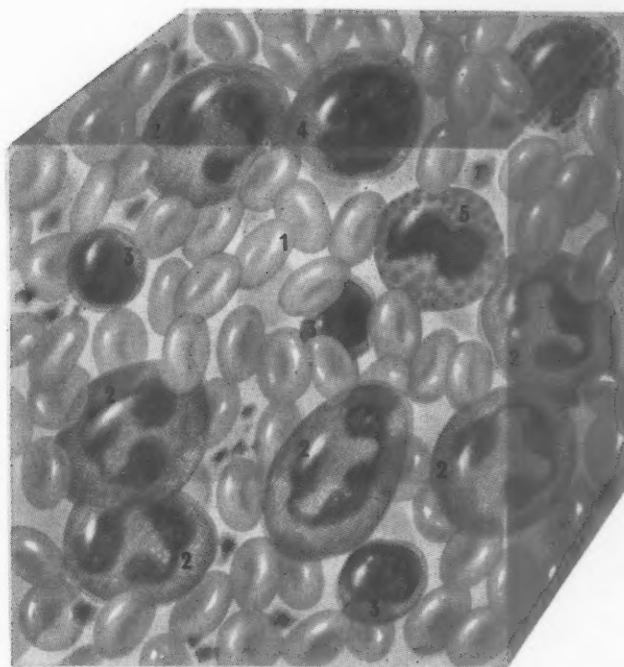
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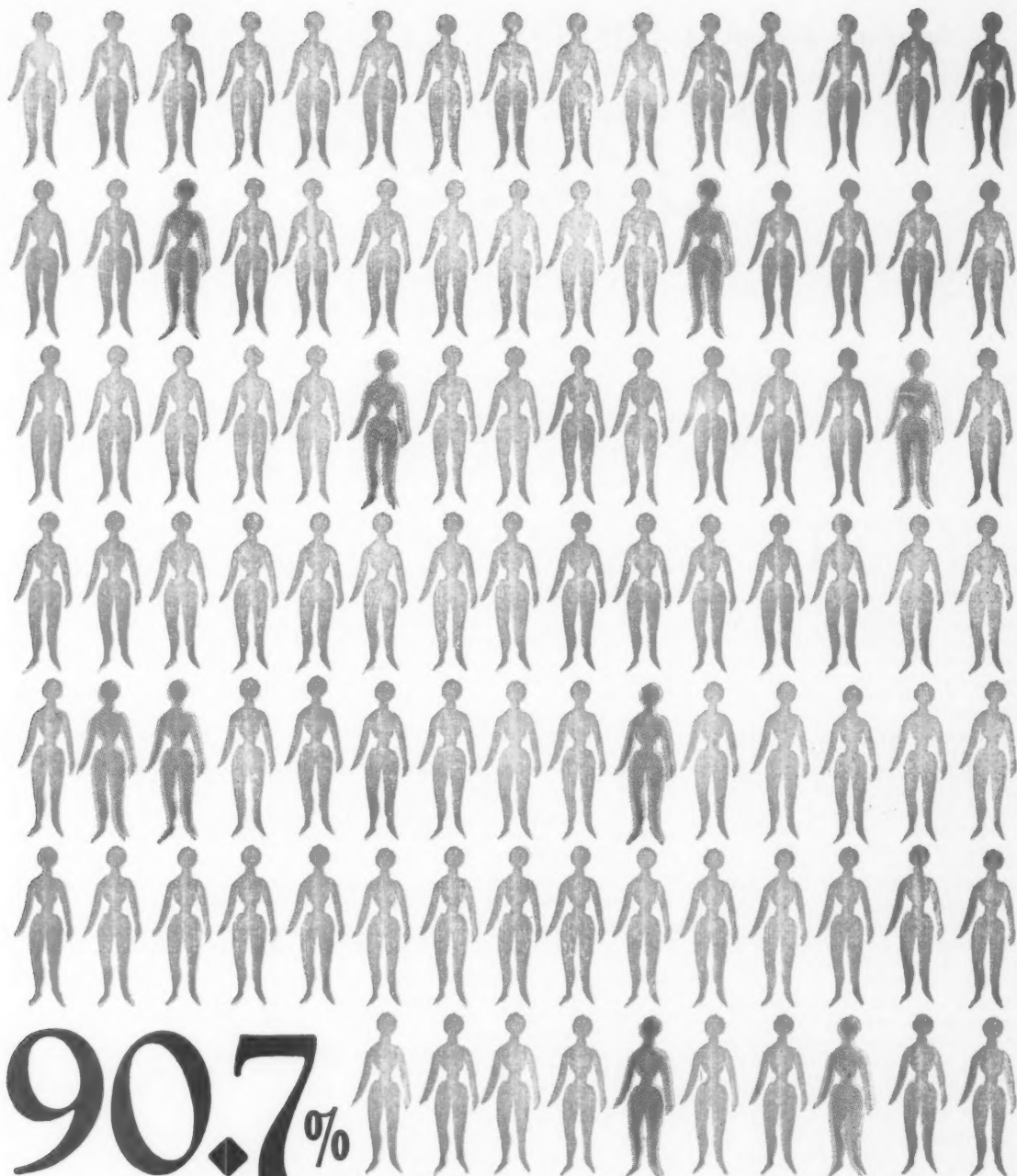
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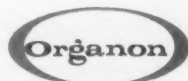
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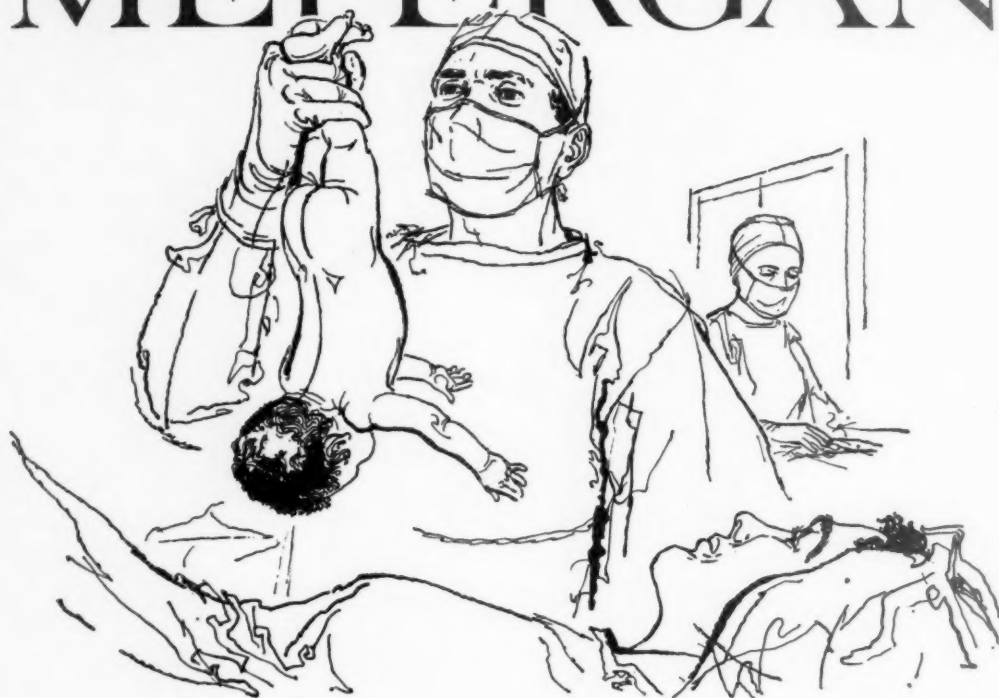
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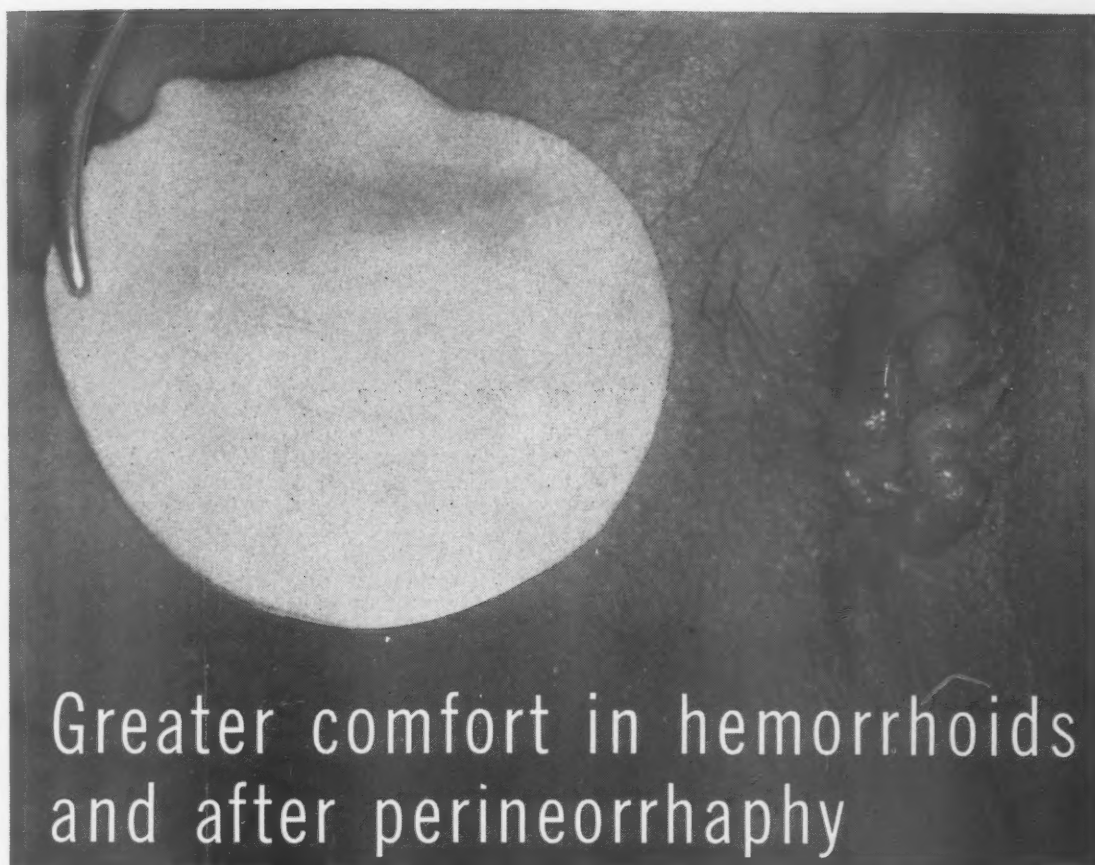
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References: 1. Rothman, E., Bentley, W.G., and Floyd, W.S.: Am. J. Obst. & Gynec. 78:38, 1959. 2. Stone, M.L., Sedlis, A., and Zuckerman, M.: *ibid.* 76:544, 1958. 3. Sands, R.X.: Canad. M.A.J. 78:935, 1958.

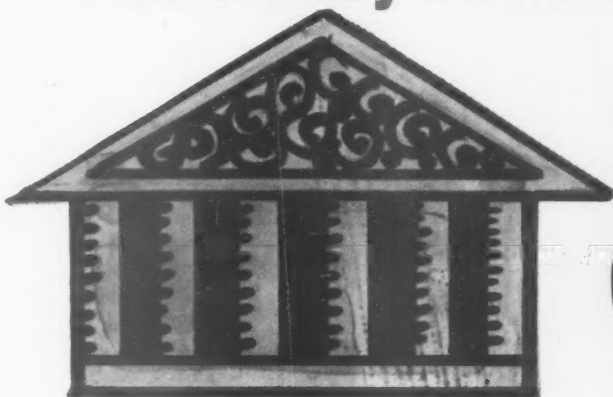
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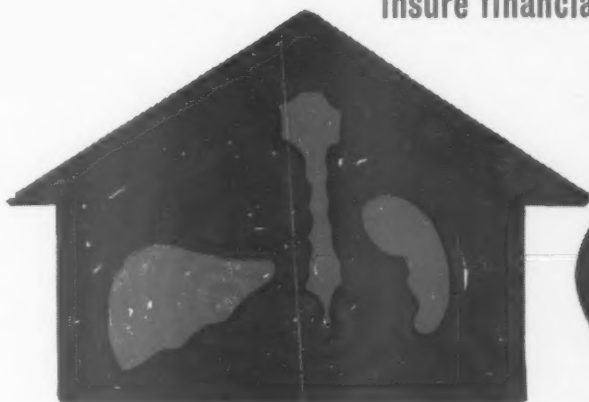
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(1) Holly, R. G.: Postgrad. Med. 26:418, 1959. (2) Evans, L. A. J., in Wallerstein, R. O., and Mettler, S. R.; Iron in Clinical Medicine, Berkeley, Univ. California Press, 1958, p. 170. (3) Schwartz, L.; Greenwald, J. C., and Tendler, D.: Am. J. Obst. & Gynec. 75:829, 1958.

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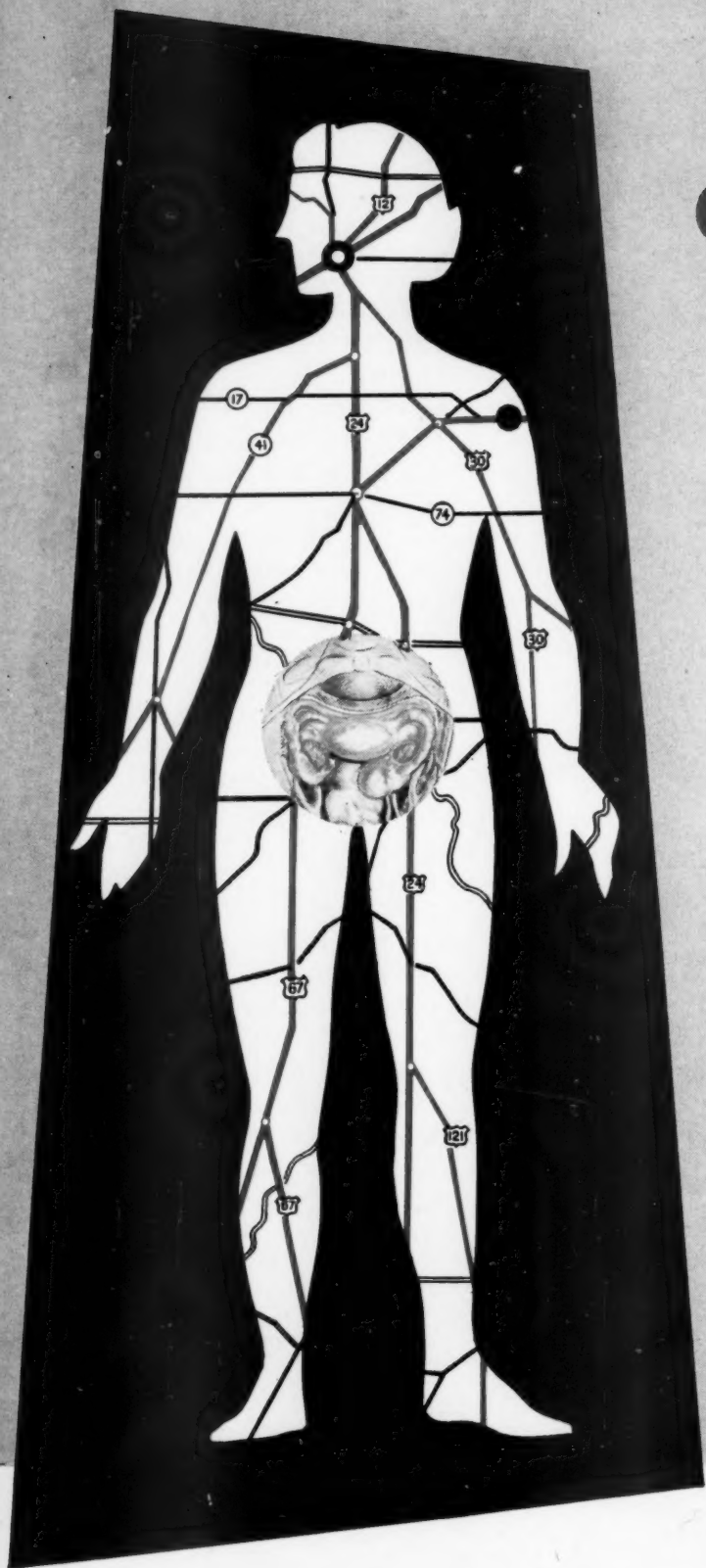
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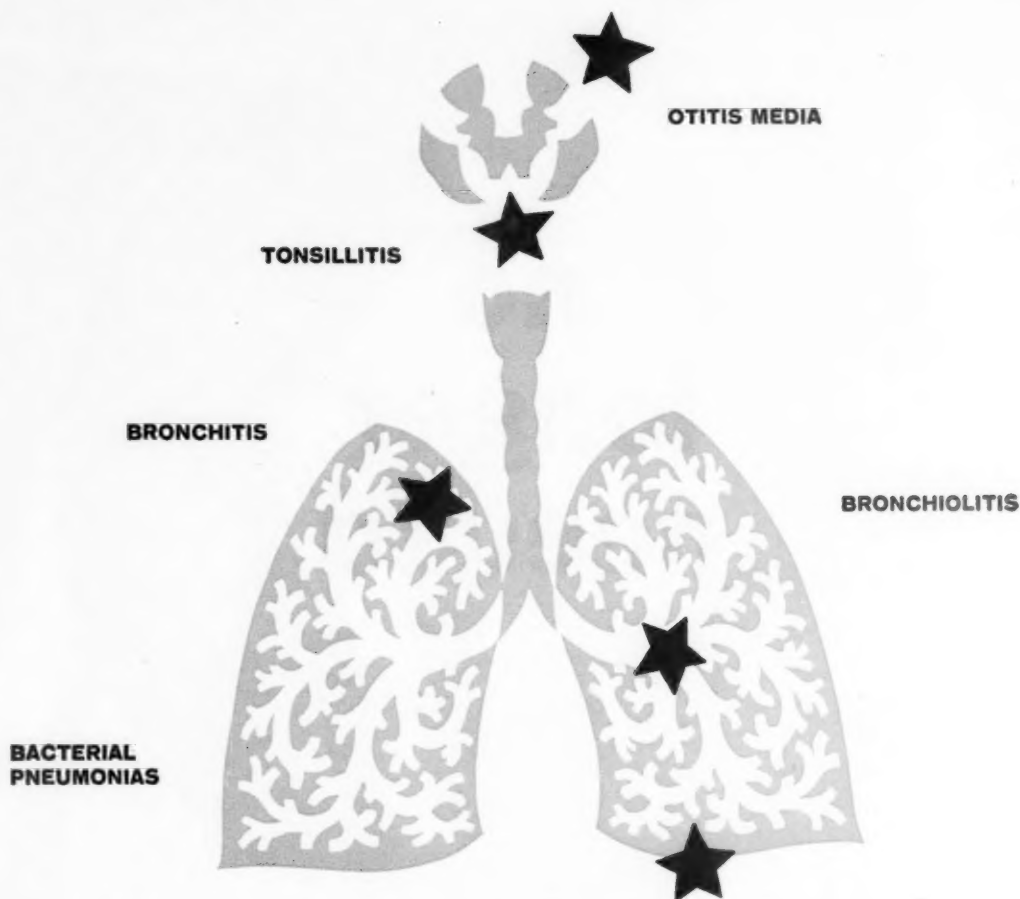
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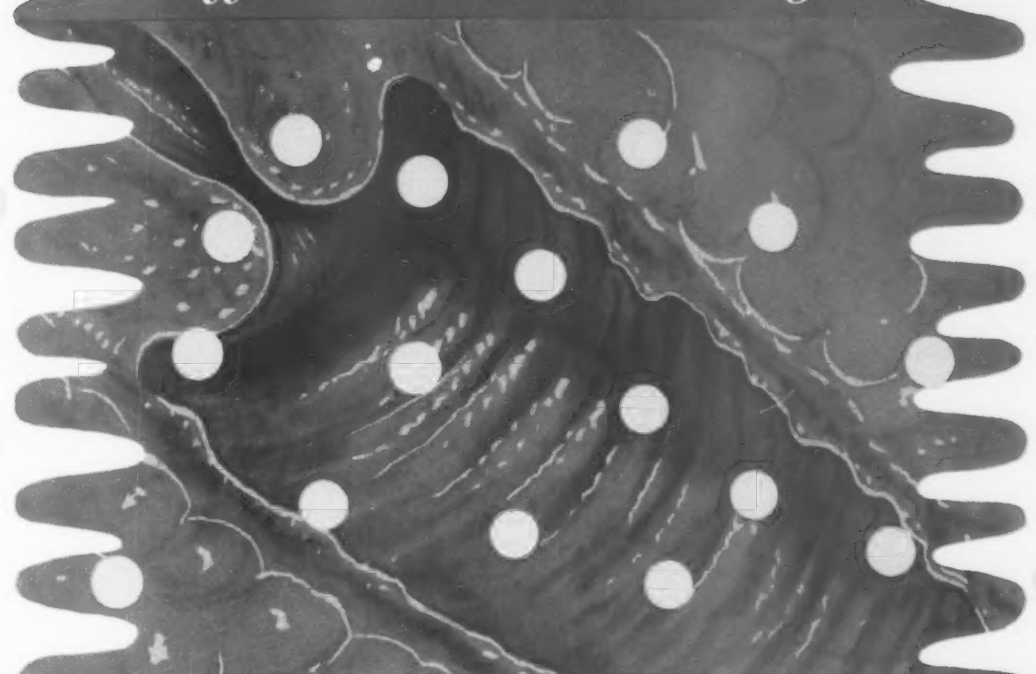
1. Ausman, D. C.: J. Am.
Geriatric Soc. 7:268, 1959.

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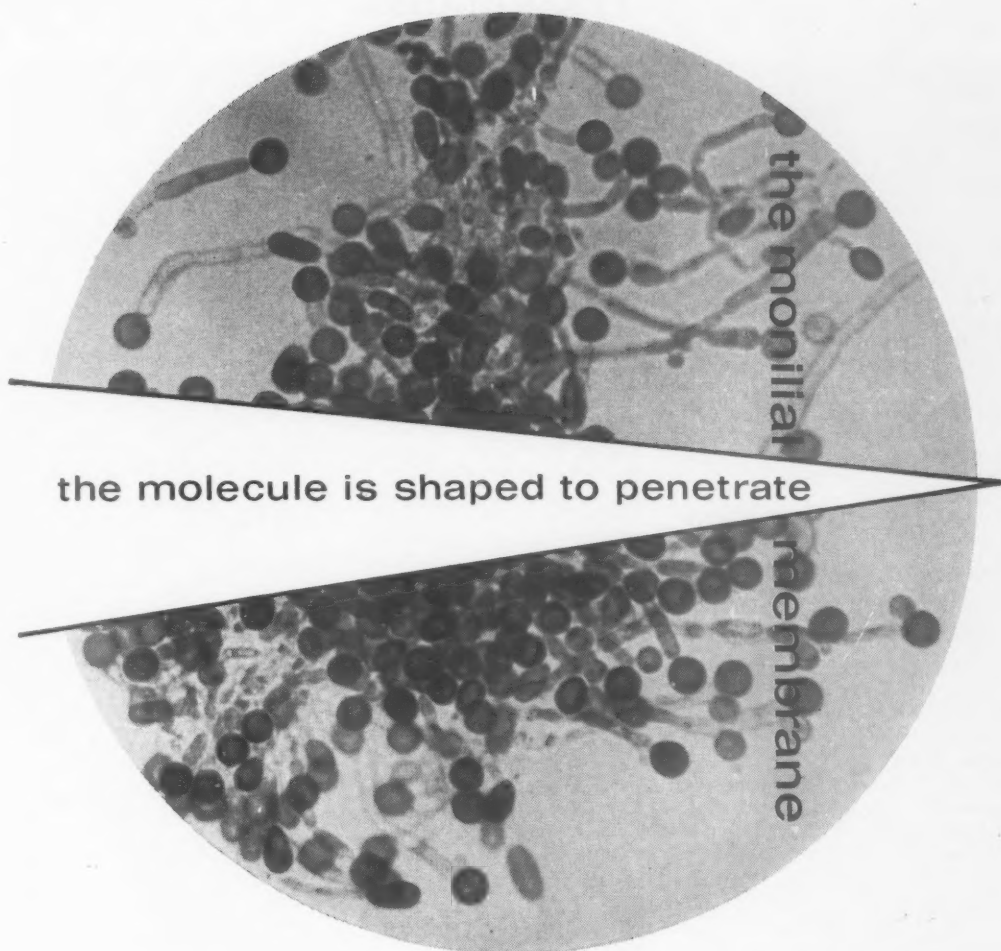
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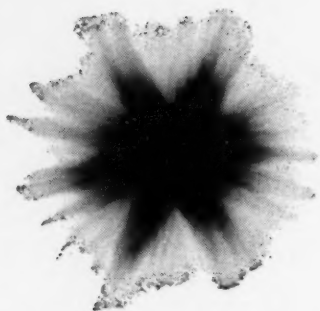
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*Lapan, B.: Am. J. Obst. & Gynec. 78:1320, 1959.





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References: 1. Trussell, R. E.: New York Med. 13:717 (Sept. 20) 1957. 2. Karnaky, K. J.: South. M. J. 51:925 (July) 1958. 3. Decker, A.: New York J. Med. 57:2237 (July 1) 1957. 4. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 5. Weiner, H. H.: Clin. Med. 5:25 (Jan.) 1958.

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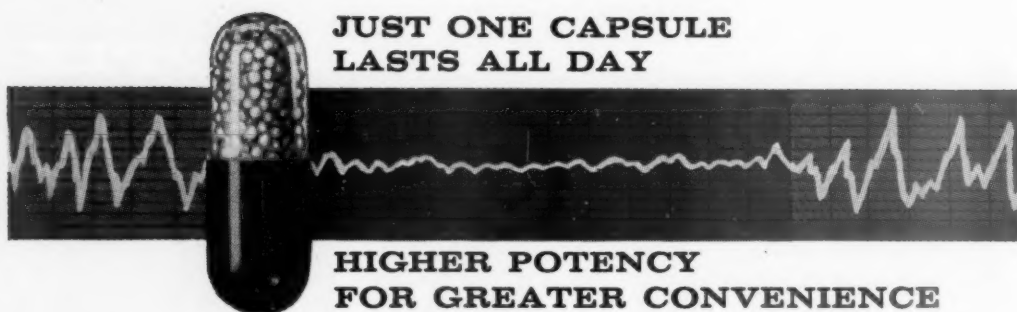
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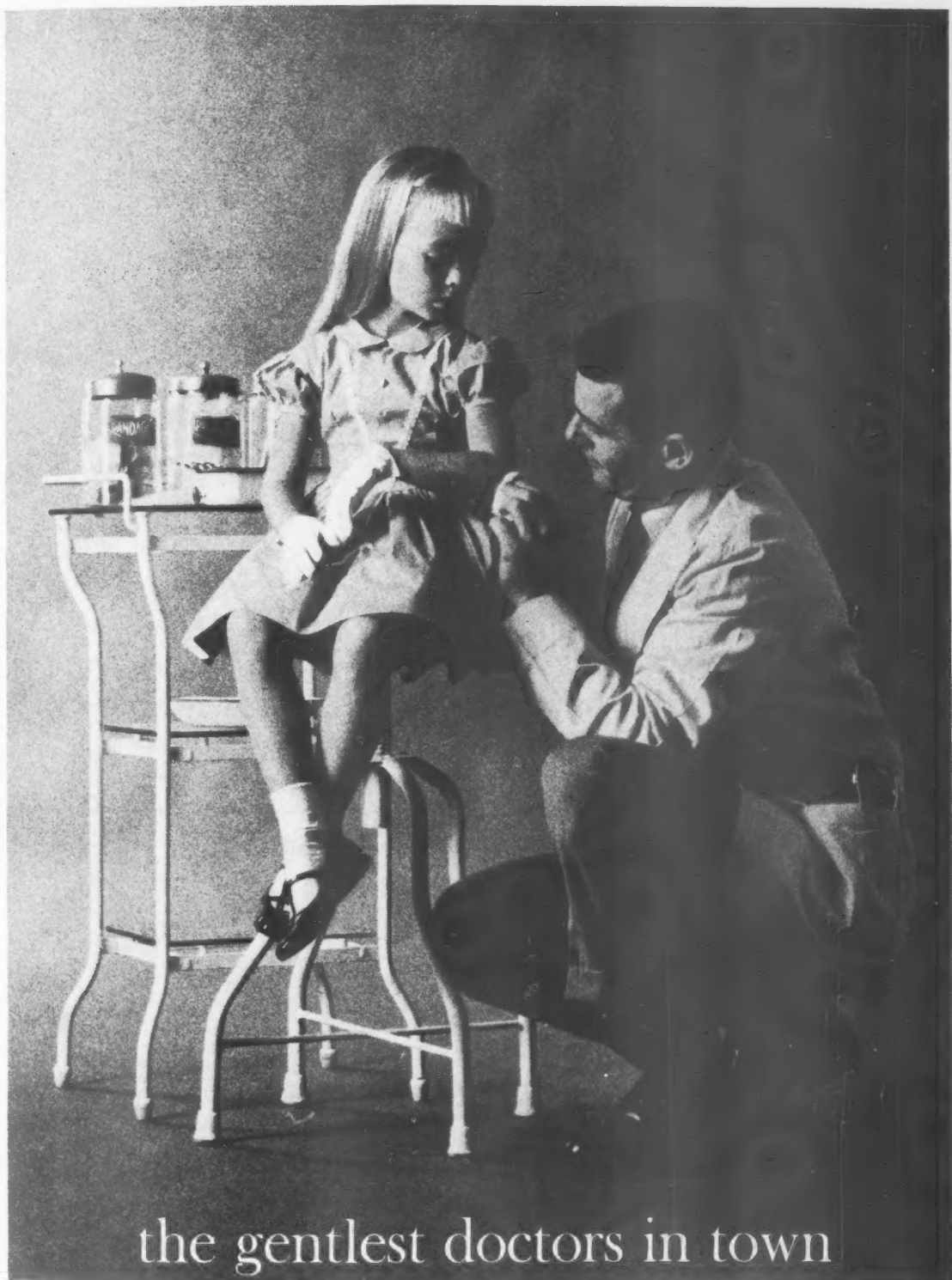
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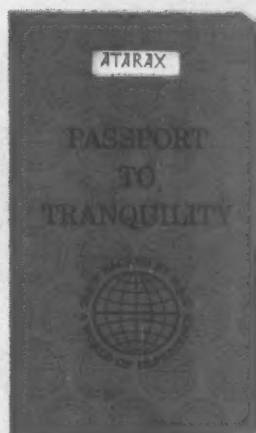
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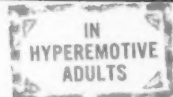
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"... seems to be the agent of choice in patients suffering from removal disorientation, confusion, conversion hysteria and other psychoneurotic conditions occurring in old age." Smigel, J. O., et al.: *J. Am. Geriatrics Soc.* 7:61 (Jan.) 1959.

"All [asthmatic] patients reported greater calmness and were able to rest and sleep better... and led a more normal life... In chronic and acute urticaria, however, hydroxyzine was effective as the sole medication." Santos, I. M., and Unger, L.: Presented at 14th Annual Congress, American College of Allergists, Atlantic City, New Jersey, April 23-25, 1958.

"... especially well-suited for ambulatory neurotics who must work, drive a car, or operate machinery." Ayd, F. J., Jr.: *New York J. Med.* 57:1742 (May 15) 1957.

...and for additional evidence

Bayart, J.: *Acta paediat. belg.* 10:164, 1956. Ayd, F. J., Jr.: *California Med.* 87:75 (Aug.) 1957. Nathan, L. A., and Andelman, M. B.: *Illinois M. J.* 112:171 (Oct.) 1957.

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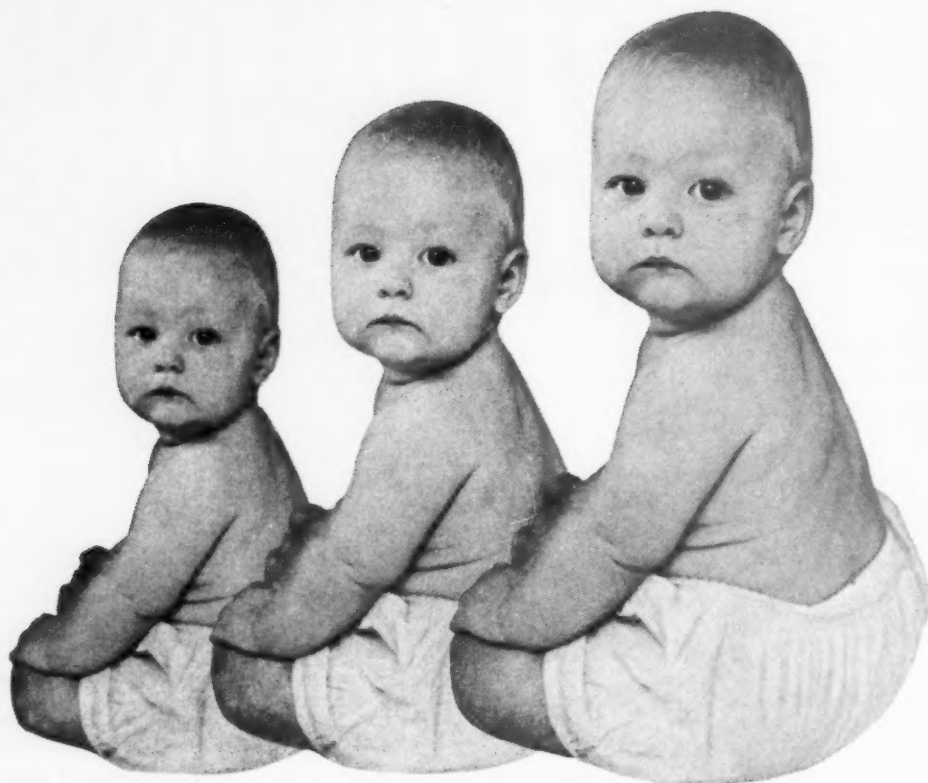
Garber, R. C., Jr.: *J. Florida M. A.* 45:549 (Nov.) 1958. Menger, H. C.: *New York J. Med.* 58:1684 (May 15) 1958. Farah, L.: *Internat. Rec. Med.* 169:379 (June) 1956.

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References: 1. Sturgeon, P., in Wallerstein, R. O., and Mettier, S. R.: Iron in Clinical Medicine, Los Angeles, University of California Press, 1958, p. 183. 2. Smith, N. J., and Schulz, J., op cit., p. 65.



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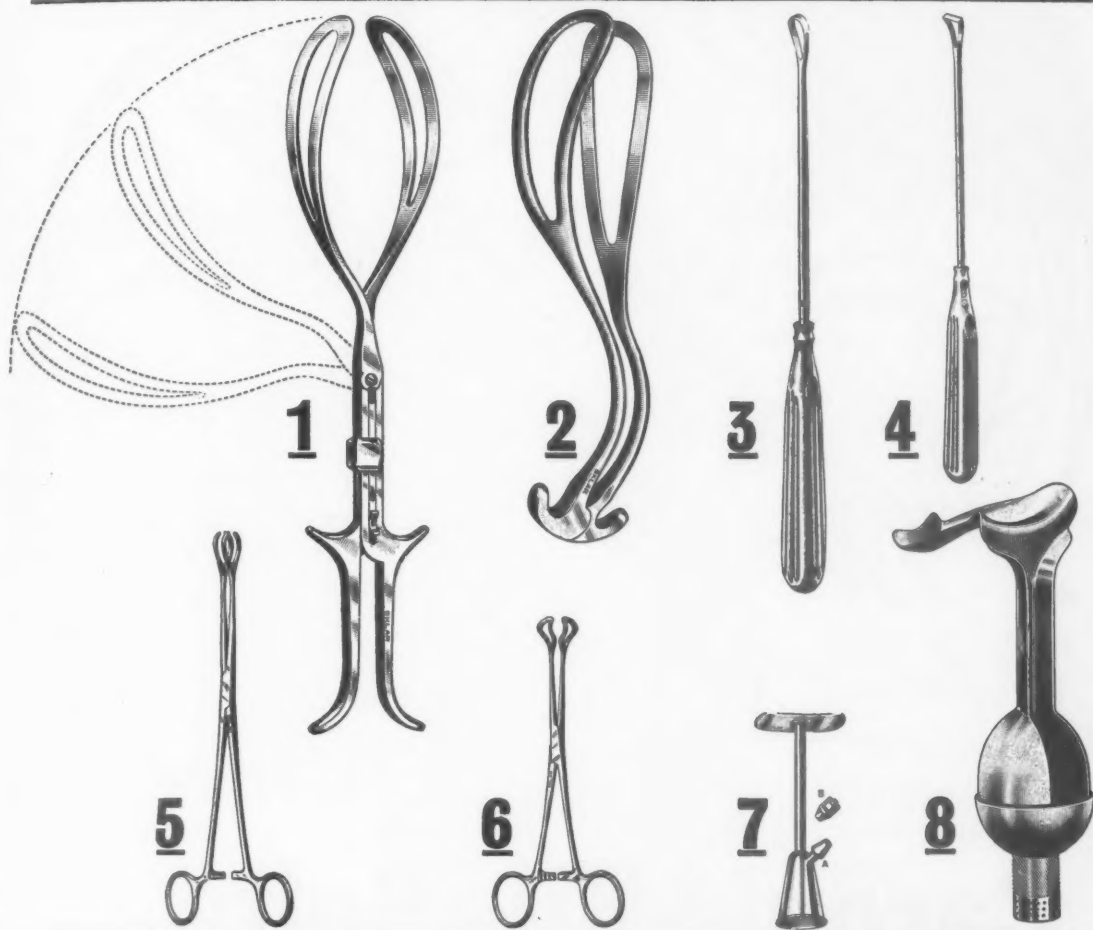
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5. Gutglass Cervix Hemostatic Forceps / provides more effective hemostasis for cervical lacerations by permitting the sutures to be placed inside ring of jaws.
6. Bunim Urethral Clamp / facilitates fixation of the urethra to the periostium of the retropubis in Marshall-Marchetti procedure.
7. Perell Fetoscope / for auscultation of fetal heart tones. Available in Luer-Lok and slip-on models; may be used with any Bowles Type Stethoscope.
8. Mason Auvard Vaginal Speculum / with specimen cup; extra long concave blade prevents slipping from vagina.



**"Because Caroid and Bile Salts Tablets are not harsh,
but act gently to produce a normal bowel movement,
I prefer them for my 'over 40' patients."**



Caroid & Bile Salts Tablets

The combined action of the principal ingredients in Caroid and Bile Salts Tablets provides 3-way, physiologic relief of constipation.

Caroid® — potent proteolytic enzyme for improved protein digestion.

Bile salts — choloretic for treatment of biliary stasis; hydrotropic for soft, well-formed stools.

Stimulaxant — to improve smooth muscle tone, restore regularity.

Dosage: 1 or 2 Caroid and Bile Salts Tablets should be taken with at least 1 glass of water about 2 hours after breakfast and at bedtime.

Samples on Request.

American Ferment Co., Inc., 1450 Broadway, New York 18, N. Y.



AFTER THE BLESSED EVENT

DERMOPLAST[®] AEROSOL

SOOTHING TOPICAL ANESTHETIC • BACTERICIDAL • FUNGICIDAL SPRAY

APPLIED WITHOUT TOUCHING THE INVOLVED SENSITIVE AREAS—*Immediate relief of pain and itching is experienced*

Formula: benzocaine 4.5%
benzethonium chloride 0.1%;
menthol 0.5%; dissolved in
oils (DOHO PROCESS)

Available in 3 sizes:

PRESCRIPTION: new 3 oz.
(for individual therapy
in hospital & home)

HOSPITAL: 12 oz. economy

JUNIOR: 6 oz.



Other indications responding
to DERMOPLAST's quick,
therapeutic pain relief:

perineal suturing
hemorrhoids
pruritus vulvae
wounds
burns
abrasions
sunburn

Supporting clinical data on request

MALLON DIVISION OF **DOHO**
100 VARICK ST., NEW YORK 13, N. Y.

for vaginal discharges!

NYLMERATE

NYLMERATE JELLY

*a proven effective agent
in treating*

TRICHOMONAS VAGINALIS VAGINITIS AND BACTERIAL VAGINITIS

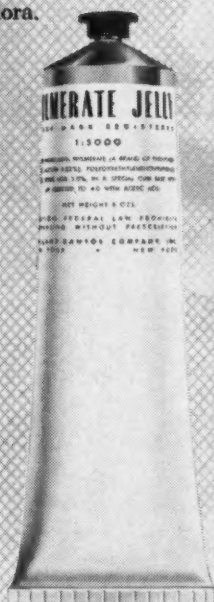
Low surface tension allows for deep
epithelial cell penetration. Kills
most offending pathogens and
re-establishes normal vaginal flora.

Prescribe: "Nylmerate Jelly
with applicator"—5 oz. tube,
also available in refill
tube only. Simple to use

... Applicator-full
intravaginally morning and
night preceded by a
Nylmerate Solution
water douche. Include
treatment through
menstrual period.
Available only
on your prescription.

ACTIVE INGREDIENTS

Polyoxyethyleneoxyphenol 0.10%
Phenylmercuric Acetate 0.02%
Boric Acid 1.0%
In a gum base with pH adjusted to 4



NYLMERATE SOLUTION CONCENTRATE

*a therapeutic vaginal
douche of choice*

Excellent adjunct in the
management of monilia and
trichomonas vaginal infections.

Restores normal vaginal flora
through a 3-prong attack.

Low surface tension aids in
reaching the innermost
recesses where organisms
flourish. Unlike vinegar, affords
a controlled pH of 4.1 in
dilution and is effective
in any vaginal pH. Broad
range activity against
protozoa—bacteria—and
fungi. Well suited for
office use in swabbing
vaginal vault.

Available only on your
prescription (eliminates
excessive and
unwarranted douching).

Specify—Nylmerate
Solution Concentrate
pint bottle with
measuring cap.

Prescribe two
tablespoonfuls or
one capful to two
quarts of water
twice daily.

As a prophylactic,
use once a day
through two
menses.



ACTIVE INGREDIENTS

Phenylmercuric Acetate 0.2% in a buffered solvent of
Alcohol 50%, Acetone 10% and de-ionized water q.s.,
added certified color with pH adjusted to 4.9.

Literature available



HOLLAND-RANTOS CO., INC.

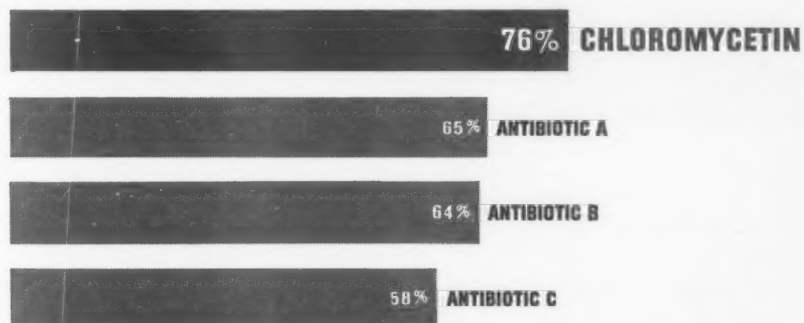
145 HUDSON STREET • NEW YORK 13, N. Y.

Time
after
time...
in study
after
study

CHLOROMYCETIN[®]

PROVES OUTSTANDINGLY EFFECTIVE AGAINST PROBLEM PATHOGENS

IN VITRO SENSITIVITY OF GRAM-POSITIVE COCCI FROM 5,600 CONSECUTIVE CULTURES
TO CHLOROMYCETIN AND TO THREE OTHER BROAD-SPECTRUM ANTIBIOTICS*



*Adapted from Leming, B. H., Jr., & Flanigan, C., Jr., in Welch, H., & Marti-Ibáñez, F.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 414.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals[®] of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.



PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

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*new
infant
formula*

Enfamil*

*nearer to mother's milk¹
in nutritional breadth
and balance*

In a well controlled institutional study,² Enfamil was thoroughly tested in conjunction with three widely used infant formula products. The investigators report: ■ good weight gains ■ soft stool consistency ■ normal stool frequency

NEARER to mother's milk . . . in caloric distribution of protein, fat and carbohydrate

NEARER to mother's milk . . . in vitamin pattern (plus more vitamin D added in accordance with NRC recommendations)

NEARER to mother's milk . . . in osmolar load

ENFAMIL IS ALMOST IDENTICAL with mother's milk in . . .

- ratio of unsaturated to saturated fatty acids
- absence of measurable curd tension . . . enhances digestibility

Enfamil contains oleo and vegetable fats . . . does not result in sour regurgitation

1. Macy, I. G.; Kelly, H. J., and Sloan, R. E.: With the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks, National Academy of Sciences, National Research Council, Publication 254, Revised 1953. 2. Brown, G. W.; Tuholski, J. M.; Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Evaluation of Prepared Milks in Infant Nutrition, Use of the Latin Square Technique. To be published.

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Mead Johnson
Symbol of service in medicine



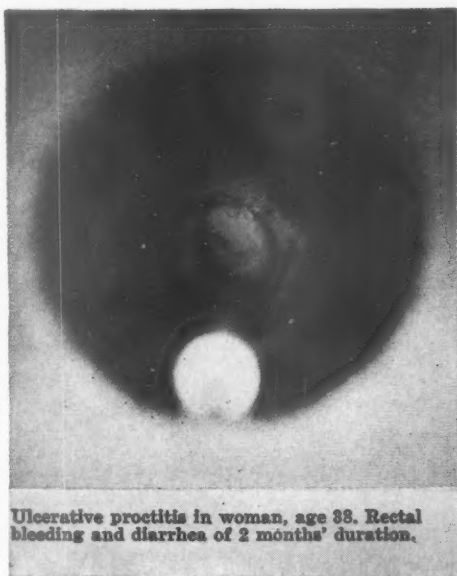
in rectal inflammation: topical hydrocortisone brings objective improvement

*dramatic decrease in bleeding, discharge, tenesmus...
visible mucosal repair*

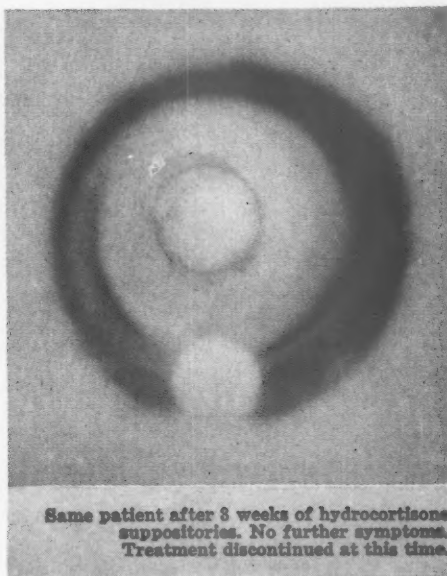
More than 90 per cent of 37 patients with radiation proctitis showed pronounced improvement when treated topically with hydrocortisone.¹ In nonspecific proctitis with bleeding and ulceration, 1 to 3 weeks of topical hydrocortisone therapy produced marked relief or complete remission.²

Because rectal absorption of hydrocortisone is minimal,¹ easy-to-use CORT-DOME Suppositories, while exerting potent local anti-inflammatory action, are virtually free of unwanted systemic corticosteroid effects...require no special precautions, except in the presence of rectal infection.

CORT-DOME[®] 25 mg. Suppositories
high potency hydrocortisone in ACID MANTLE[®] vehicle **DOME** pH 5.4



Ulcerative proctitis in woman, age 38. Rectal bleeding and diarrhea of 2 months' duration.



Same patient after 3 weeks of hydrocortisone suppositories. No further symptoms. Treatment discontinued at this time.

Indicated in postirradiation (factitial) proctitis; nonspecific proctitis; chemical and medicinal proctitis; as an adjunct in treatment of chronic ulcerative colitis; cryptitis; other inflammatory conditions of anorectum.

Available in boxes of 12. Each foil-wrapped suppository contains 25 mg. hydrocortisone alcohol in a nonirritating ACID MANTLE[®] vehicle.

1. Kaplan, B. J.: Connecticut State M. J. 20:357, 1956. 2. Kaplan, B. J.: Personal communication.



DOME CHEMICALS INC. 125 West End Ave., New York 23, N. Y.
Los Angeles • Montreal

In the menopause...
transition without tears



**Milprem promptly relieves emotional distress
 with lasting control of physical symptoms**

Milprem®

Miltown®+conjugated estrogens (equine)

Supplied in two potencies for dosage flexibility:

MILPREM-400, each coated pink tablet contains 400 mg. Miltown (meprobamate) and 0.4 mg. conjugated estrogens (equine).

MILPREM-200, each coated old-rose tablet contains 200 mg.

Miltown and 0.4 mg. conjugated estrogens (equine).

Both potencies in bottles of 60.

Literature and samples on request.

In minutes, Milprem starts to ease anxiety and depression. It relieves insomnia, relaxes tense muscles; alleviates low back pain and tension headache. As the patient continues on Milprem, the replacement of estrogens checks hot flushes and other physical symptoms.

Easy dosage schedule: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.



WALLACE LABORATORIES, New Brunswick, N. J.

CHF-3224-69

*the true specific
for
monilial vaginitis*

GENTIA-JEL®

CURES ARE QUICKER Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrence. **IMMEDIATE RELIEF** This soothing gel provides fast, gratifying relief of vulvar itching and burning . . . destroys fungi and bacteria. **COMPLETE COVERAGE** Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia.



*start therapy
with GENTIA-JEL
. . . it works
when others fail*

WESTWOOD PHARMACEUTICALS

Buffalo 13, New York

GENTIA-JEL

*the true specific
for monilial vaginitis*

Gentian violet is the most effective agent known for the destruction of *Monilia albicans*. Numerous nonstaining preparations have been used in treating vaginal moniliasis but have proven far less effective than gentian violet.

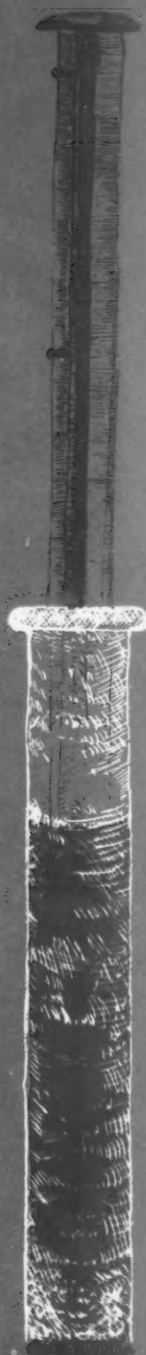
Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monilial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never reused, but discarded.

And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.



**WHY WAIT UNTIL OTHER THERAPIES FAIL . . .
START YOUR PATIENTS WITH GENTIA-JEL**

WESTWOOD PHARMACEUTICALS

Buffalo 13, New York

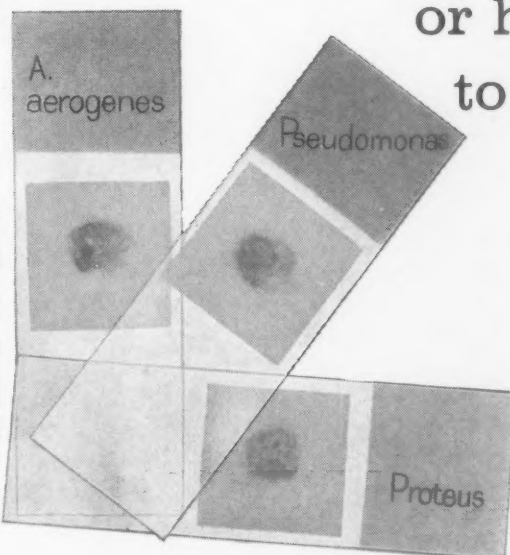
DECLOMYCIN[®] NOTES:

Demethylchlortetracycline Lederle

pathogen

sensitivity

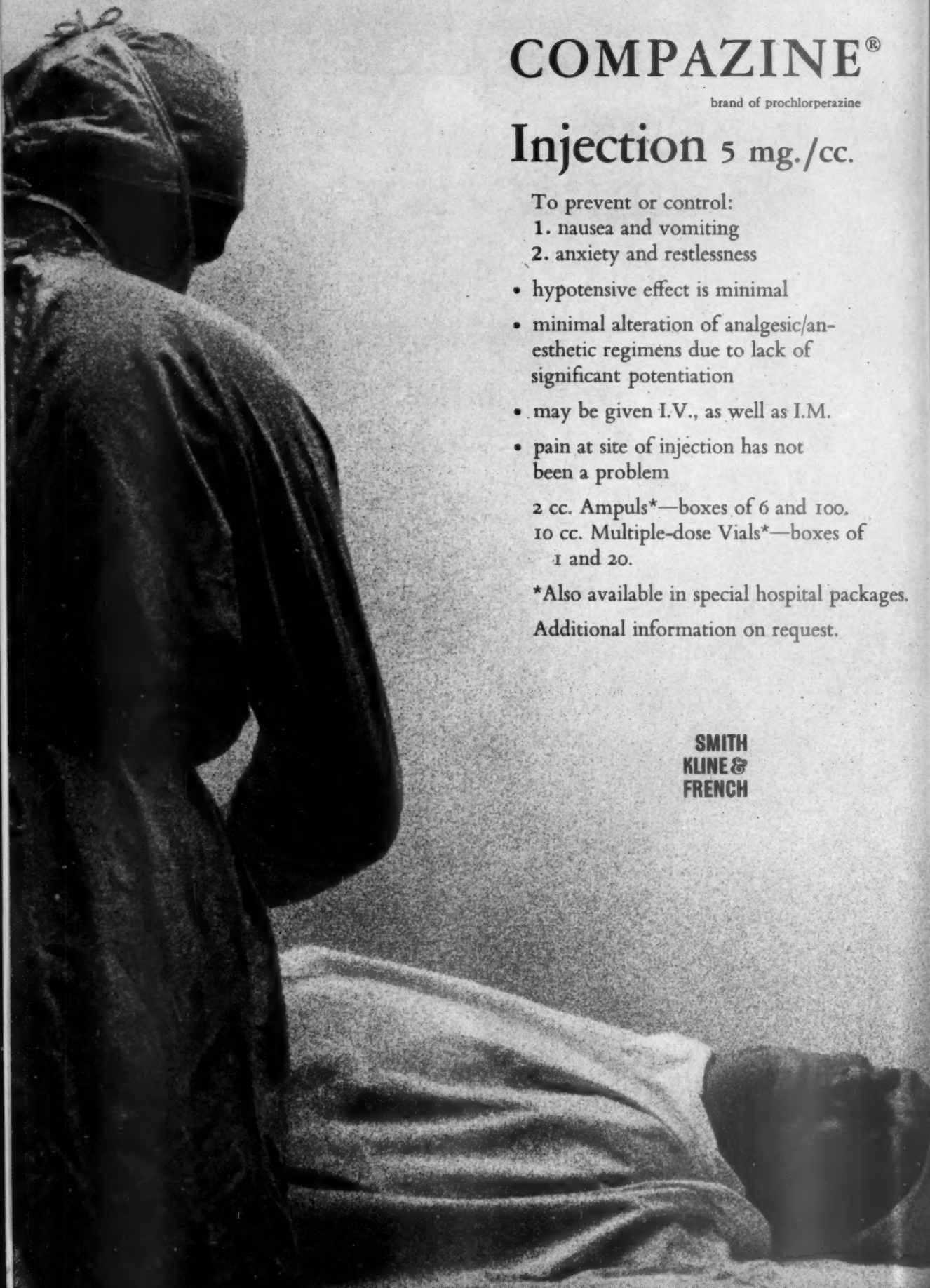
In addition to the expected broad-spectrum range of effectiveness, DECLOMYCIN has demonstrated activity against strains of *Pseudomonas*, *Proteus* and *A. aerogenes*¹⁻⁵ unresponsive refractory antibiotics. or highly to other



1. Department of Clinical Investigation, Lederle Laboratories, F. M. Phillips, Director. Interim Report on Clinical and Pharmacologic Investigations. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A.; Kunin, C. M., and Finland, M.: *München. med. Wchnschr.* To be published. 4. Roberts, M. S.; Seneca, H., and Lattimer, J. K.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 5. Vineyard, J. P.; Hogan, J., and Sanford, J. P.: *Ibid.* Capsules, 150 mg.—Pediatric Drops, 60 mg./cc.—Oral Suspension, 75 mg./5 cc. tsp.

GREATER ACTIVITY... FAR LESS ANTIBIOTIC... SUSTAINED-PEAK CONTROL... "EXTRA-DAY" PROTECTION AGAINST RELAPSE

 LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y



before, during, or after surgery

COMPAZINE[®]

brand of prochlorperazine

Injection 5 mg./cc.

To prevent or control:

1. nausea and vomiting
2. anxiety and restlessness

- hypotensive effect is minimal
- minimal alteration of analgesic/anesthetic regimens due to lack of significant potentiation
- may be given I.V., as well as I.M.
- pain at site of injection has not been a problem

2 cc. Ampuls*—boxes of 6 and 100.

10 cc. Multiple-dose Vials*—boxes of 1 and 20.

*Also available in special hospital packages.

Additional information on request.

**SMITH
KLINE &
FRENCH**

RECOMMENDED READING IN OBSTETRICS AND GYNECOLOGY

A TEXTBOOK OF GYNECOLOGY by Laman A. Gray, *University of Louisville Medical School*. A fresh and stimulating text—emphasizing points in **PATHOLOGY, DIAGNOSIS, and TREATMENT**. Theories are touched upon but the theme always returns to the facts as known today. Tone drawings, sketches, photomicrographs—all are **NEW AND ORIGINAL**, created especially for this book by artist **JEAN HELLSTROM**. The integrated understanding of a woman's personality and its effect on her gynecologic function, and vice versa, are touched upon importantly throughout the book. Pub. Feb. '60, 484 pp. (8½ x 11), 344 il., \$15.50

GYNECOLOGICAL UROLOGY. Edited by Abdel Fattah Youssef, *Cairo University, Egypt*. With contributions by thirty-two leading specialists from eight countries, this is by far the most comprehensive and up-to-date work on gynecological urology that exists in any language. Covers all interrelated aspects of the two specialties with particular emphasis on recent trends and developments including a thorough discussion of urologic problems in obstetrics. Clearly a reflection of modern medical opinion throughout the world—a magnificent illustration of what can be achieved in the field of medical writing by international cooperation on a large scale. Publication date May 1960

CARCINOMA IN SITU OF THE UTERINE CERVIX: A Study of 235 Cases from the Free Hospital for Women by Gilbert H. Friedell, Arthur T. Hertig, and Paul A. Younge, *all of Harvard Medical School, Boston*. **PURPOSE:** To clearly delineate the pathological entity carcinoma in situ from benign conditions on the one hand and invasive carcinoma on the other. Covers historic background, cases of carcinoma in situ progressing to invasive carcinoma, pathologic anatomy, clinical findings, and cytology. Copiously illustrated. Publication date May 1960


OXYGEN SUPPLY TO THE HUMAN FOETUS. A symposium organized by the Council for International Organizations of Medical Sciences and edited by James Walker with the assistance of Alec C. Turnbull, *both of the University of St. Andrews*. A group of expert respiratory physiologists, clinical pediatricians, and obstetricians pool their experience and specialized knowledge. The full range of current experimental work is presented and analyzed from the **experimental, technical, physiological, and clinical viewpoints**. The result is an essential basic text for the research worker and clinician in this rapidly expanding area of knowledge. Pub. Dec. '59, 346 pp., 137 il., \$10.50

A SHORT HISTORY OF OBSTETRICS AND GYNECOLOGY by Theodore Cianfrani, *University of Pennsylvania, Philadelphia*. Here is the "meat" of the specialty to be read with the greatest interest and with minimal effort. One part leads to the next in regular sequence with enough of the human element included to make **fascinating reading**. Pages on the 19th century form an important section on progress. *Particularly outstanding are the illustrations which accompany the chapter on "Primitive Obstetrics and Gynecology."* Publication date April 1960

LIBIDO by J. E. Schmidt, *Charlestown, Indiana*. Using his original "reversicon" presentation, Doctor Schmidt brings together for the first time the substance of the scientific or learned terminology and the bulk of the esoteric slang which constitute the vocabulary of sex and libido. **PURPOSE:** To serve as a guide to the meaning of some 7,000 common word expressions. Without this dictionary a whole underworld of life and living could not be interpreted or understood by the professional groups concerned. Available direct from the publisher only. When ordering please indicate professional status to aid the publisher in screening orders. Pub. Jan. '60, 288 pp., \$8.00

CHARLES C THOMAS • PUBLISHER 301-327 East Lawrence Avenue SPRINGFIELD • ILLINOIS

**in premenstrual
tension**



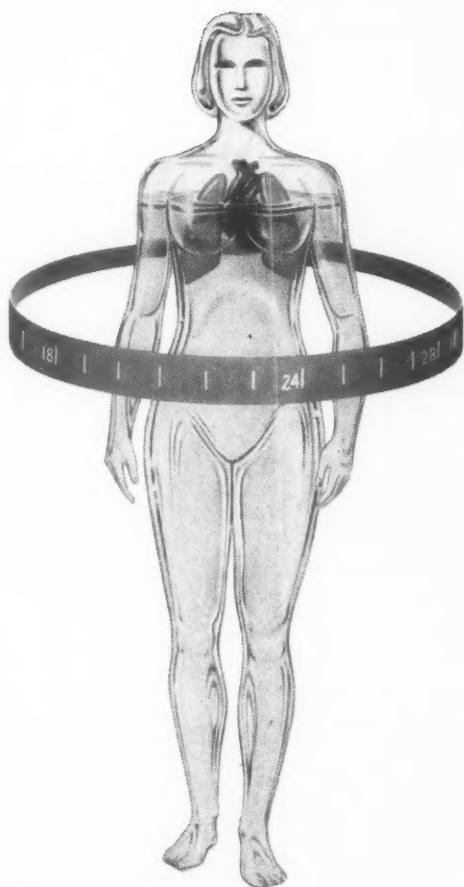
**clinicians report
rapid relief with**

HYDRODIURIL[®]

HYDROCHLOROTHIAZIDE

increased potency—without corresponding increase in side effects

*Fuchs, M. and Moyer, J.:
Diseases of the Chest 35:314, (March) 1959.*



“Premenstrual edema is present in 40% of women and...consists of weight gain, subcutaneous edema, emotional lability, breast turgidity, anxiety and tension.” In addition to controlling the objective symptoms of premenstrual tension, HYDRODIURIL may afford relief of subjective complaints including tension, nervousness and headache.

DOSAGE: 25 to 50 mg. of HYDRODIURIL once or twice a day, beginning the first morning of symptoms and continuing until the onset of the menses.

SUPPLIED: 25 and 50 mg. scored tablets HYDRODIURIL (hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., Inc.

Additional information on HYDRODIURIL is available to the physician on request.



MERCK SHARP & DOHME
Division of Merck & Co., Inc. West Point, Pa.

FOUND: a dependable solution to

"the commonest gynecologic office problem"

"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . ."

Ensey, J. E.: Am. J. Obst. 77:155, 1959

TRICOFURON[®]

Improved

- Swiftly relieves itching, burning, malodor and leukorrhea
- Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis ■ Achieves clinical and cultural cures where others fail ■ Nonirritating and esthetically pleasing

2 steps to lasting relief:

1. POWDER for weekly insufflation in your office. MICOFUR[®], brand of nifuroxime, 0.5% and FUROXONE[®], brand of furazolidone, 0.1% in an acidic water-dispersible base.
2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

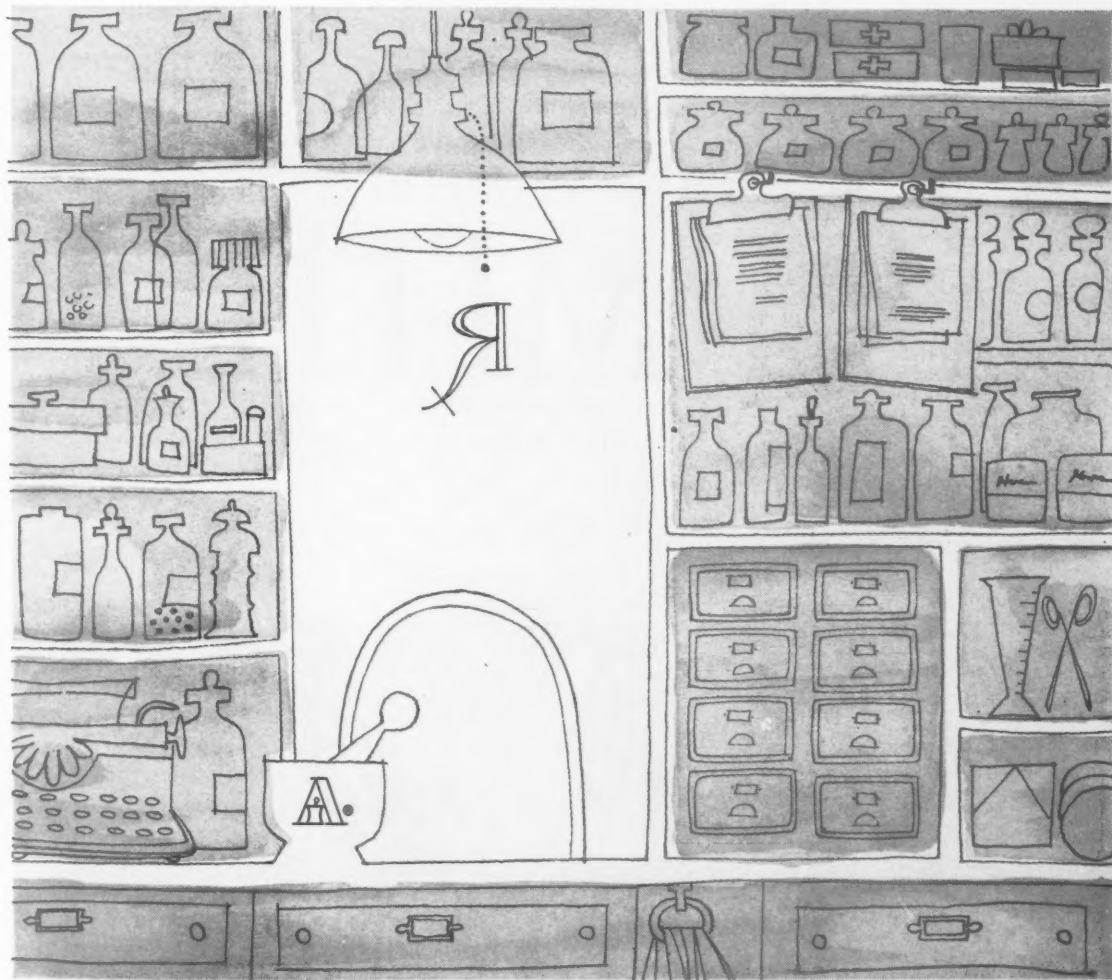
*Rx new box of 24 suppositories with applicator
for more practical and economical therapy.*

NITROFURANS—a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

NO OTHER THYROID PRODUCT

is used so widely and so often . . . stocked by so many leading pharmacies . . . regarded throughout the world as the pioneer in thyroid standardization and the original standard of comparison for all thyroid preparations

ALWAYS SPECIFY ARMOUR THYROID



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Armour Means Protection

**90% of anxious, agitated
and apathetic office patients
calmed without drowsiness
and with normal drive restored...**

on one or two 0.25 mg. tablets b.i.d.:

This is the pattern of performance for

PERMITIL[®]

Fluphenazine dihydrochloride

In Anxiety and Anxiety-induced Depression

"In contrast to other phenothiazines, it [PERMITIL] mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."¹

- In 608 patients with anxiety and anxiety-induced fatigue or depression, PERMITIL, administered in small daily doses of 0.5 mg. to 1 mg., produced significant improvement in 90%.²
- PERMITIL is virtually free from side effects at recommended dosage levels.
- Patients become calm without being drowsy and normal drive is restored.
- Onset of action is rapid; effect is prolonged.
- PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

How to prescribe PERMITIL: The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

SUPPLIED: Tablets, 0.25 mg., bottles of 50 and 500.

REFERENCES: 1. Ayd, F. J., Jr.: *Current Therapeutic Research* 1:41 (Oct.) 1959.
2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.



PERMITIL

White

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

GREATER PATIENT COMFORT and safety with **DYCLONE™** dyclonine hydrochloride

the unsurpassed topical anesthetic

for
instrumentations
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DYCLONE does more...safely...than any
other topical anesthetic because it is

fast-acting
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antibacterial
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supply...Dyclone Creme, tubes of 1 oz. with
rectal applicator. Dyclone Solution, bottles
of 1 and 8 oz.



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Dulcolax[®]

brand of bisacodyl

Suppositories

Solely by contact with the colonic mucosa, Dulcolax reflexly produces coordinated large bowel peristalsis with resulting evacuation.

Generally a single evacuation of soft, formed stool without catharsis or straining results.

"A gentle but effective laxative"*
In tablet form Dulcolax is eminently convenient when overnight action is required. For more prompt effect Dulcolax suppositories usually act within the hour.

*Archambault, R.: Canad. M. A. J. 81:28, 1959.

Dulcolax[®], brand of bisacodyl: yellow enteric-coated tablets of 5 mg. in box of 6 and bottle of 100; suppositories of 10 mg. in box of 6.

Under license from C. H. Boehringer Sohn, Ingelheim.



Geigy, Ardsley, New York

Geigy

circumventing the enema

unique contact laxative



DU 6-60

New Enzyme-controlled antifungal therapy to meet the growing challenge of Monilial Vaginitis

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY—Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females¹—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

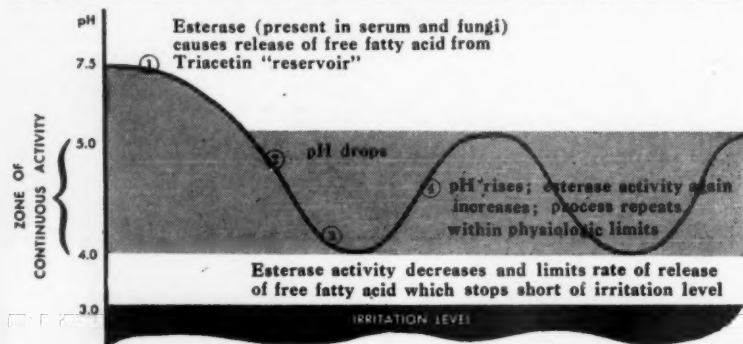
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.² Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.³

Other advantages: No monilial resistance demonstrated⁴ / prolonged duration of activity⁴ / nonsensitizing / nonirritating / nonstaining / odorless.

"VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION^{5,6}



Indications: specific in monilial vaginitis...adjunctive in trichomoniasis...also valuable in non-specific vaginitis where an acid pH must be restored and maintained.

Usual Dosage: 2 to 4 grams daily. **Supplied:** No. 204-250 mg. Glyceryl triacetate per gram in a non-liquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

References: 1. Idson, B.: Drug & Cosmetic Industry 84:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. 28:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.



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Patent Application Pending



she can choose her own silver...

but she needs **your** help in planning her family

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VAGINAL CREAM

THE MODERN CHEMICAL SPERMICIDE

Preceptin[®]
VAGINAL GEL

THE SPERMICIDAL GEL WITH BUILT-IN BARRIER

PRESCRIBED WITH CONFIDENCE FOR SIMPLE, EFFECTIVE CONTRACEPTION

confirmed in clinical study:

**MAXIMUM DIURETIC EFFECT
WITH MINIMUM TOXICITY IN
LONG-TERM EDEMA THERAPY**

ORETICTM
(Hydrochlorothiazide, Abbott)

a potent means when the end is diuresis



Studying **ORETIC**, which they describe as "... a significant advance in development of diuretic agents of greater potency without increasing toxicity..." the investigators tested, among other properties of the compound, its clinical efficiency in long-term treatment of various edematous conditions.

Twenty patients were studied: eleven cardiacs, 3 nephrotics, 2 cirrhotics, 2 pregnancies (third trimester) and 2 "steroid" edematous patients.

Drug was given in 50-mg. dosages, daily for ninety days. Observations were made in the control state, and on the seventh, twenty-first and ninetieth days. Results were computed for body weight, serum electrolytes, blood urea, nitrogen and hematocrit:

CLINICAL RESPONSES TO ORETIC IN VARIOUS EDEMATOUS STATES

(Average Values for Each Group, Dose of 50 mg. daily)

Type of Edema	Number of pts.	Period	Cumulative Weight Loss (lbs.)	Serum (mEq/L)				BUN mg%	HCT.
				Na	K	CO ₂ CP.*	Cl		
Cardiac	11	Control		139	4.4	27	107	20	44
		Day 7	4	138	4.2	29	104	22	45
		Day 21	9	136	4.1	30	103	23	46
		Day 90	14	137	4.2	30	104	25	48
Nephrotic	3	Control		132	3.6	24	93	32	41
		Day 7	5	128	3.5	26	91	30	42
		Day 21	13	125	3.3	27	90	29	44
		Day 90	19.5	127	3.3	28	90	27	45
Cirrhotic	2	Control		131	3.2	26	88	9	39
		Day 7	6	130	2.7	25	86	10	42
		Day 21	15	128	2.6	26	85	11	41
		Day 90	22	128	2.7	26	84	10	42
Pregnancy	2	Control		144	4.2	27	106	11	40
		Day 7	2	143	4.1	28	102	13	41
		Day 21	5	142	4.1	31	99	13	43
"Steroid"	2	Control		146	3.5	32	94	14	38
		Day 7	3	145	3.3	33	89	15	42
		Day 21	6	143	3.0	33	87	17	43
		Day 90	9	142	3.1	34	88	17	43

*CO₂CP—Carbon Dioxide combining power

THE INVESTIGATORS SAID:

"The drug was effective in the therapy of edema, regardless of etiology, as seen from the data . . . All the groups had significant weight loss with the greatest loss occurring in the nephrotic and cirrhotic groups: except for the relief of the edema in all the patients observed, no other changes in clinical status were observed. Persistence of diuresis and the lack of additional toxicity in long term (90 days) therapy has been observed."

ORETIC, indicated for hypertension and edema, is supplied in 25- and 50-mg. tablets, bottles of 100 and 1000.



Bibliographical Note: The study quoted has been published in the Sept., 1959, issue of *Current Therapeutic Research*, pp. 26-33.

and remember—
in many cases
ORETIC
permits relaxation
of rigid
low-sodium
diets



before, during, and after childbirth

VISTARIL®...eases mental and physical discomfort
hydroxyzine pamoate

When you give her VISTARIL, confidence replaces anxiety — but not to the point of euphoria. The effectiveness of VISTARIL in pre- and postpartum nausea and vomiting adds greatly to the patient's comfort. VISTARIL enhances the action of opiates, thus decreasing narcotic requirements and lessening the possibility of respiratory depression and reduced circulatory and cortical function.

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WHICH
ONE IS
THE
BLEEDER?

CASE NO. 1

Blood Coagulation Time
3 min. 15 sec.
Bleeding Time . 1 min. 30 sec.

CASE NO. 2

Blood Coagulation Time
3 min. 25 sec.
Bleeding Time . 1 min. 20 sec.

CASE NO. 3

Blood Coagulation Time . 3 min.
Bleeding Time . 1 min. 30 sec.

CASE NO. 4

Blood Coagulation Time
3 min. 15 sec.
Bleeding Time 2 min.

CASE NO. 5

Blood Coagulation Time
3 min. 10 sec.
Bleeding Time . 1 min. 40 sec.

All had normal blood studies—
yet one had a bleeding problem.



1



2



3



4



5

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SALICYLATE
(Brand of carbazochrome salicylate)

*U.S. Pat. Nos. 2581850, 2506294

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Bristol, Tennessee • New York • Kansas City • San Francisco

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SALICYLATE
(Brand of carbazochrome salicylate)

TO CONTROL THE MOST COMMON CAUSE OF BLEEDING

The most common cause of bleeding is increased capillary permeability, according to recent studies. Coagulative defects, the least common cause, occurred in less than one of every four patients whose chief complaint was abnormal bleeding.*

Without a history of bleeding, there is no way of determining whether a patient tends to exhibit increased capillary permeability. Therefore many surgeons administer Adrenosem preoperatively as a standard safety measure.

Adrenosem controls bleeding by decreasing excessive capillary permeability and promoting retraction of severed capillary ends. Thus it controls the chief cause of bleeding. Its high index of safety, with no contraindications at recommended dosage levels, establishes Adrenosem as a standard preventive measure, even where there is no history of abnormal bleeding.†

A VALUABLE ADJUNCT TO SURGERY

The preoperative use of Adrenosem adds an extra measure of safety during surgical procedures. It makes good technic even better, by providing a clear operative field.



*E. Cheraskin:
The Control of Bleeding,
J. Am. Dent. Assn.,
58:17 (Apr., 1959).

†Extensive bibliography
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SUPPLIED:

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TABLETS—1 and 2.5 mg.

SYRUP—each 5 cc., 2.5 mg.

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AVC IMPROVED suppositories

provide all the proven effectiveness of AVC Improved Cream in a completely new suppository form. The gelatin capsule disintegrates in 8-10 minutes; the AVC then spreads rapidly.

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have proved effective in a wide variety of vaginal conditions.^{1,7,9,11,12} The "CURE" rate with AVC Improved is consistently high.^{2-6,8,10} Irritation and itching are relieved, discharge and odor are eliminated and the causative pathogens destroyed.

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AVC IMPROVED suppositories

may be carried in the purse or pocket. They are ideal for use away from home, at work or while travelling. Easily inserted with or without applicator. Appearance and touch, not greasy or sticky, encourage patient cooperation and acceptance.

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Administration: One suppository inserted intravaginally, twice daily.

Supplied: Box of 12 suppositories with applicator.

References: 1. Peikes, I. L.: *Journal-Lancet* 79:368, 1959. 2. Cacciarelli, R. A.: *J. M. Soc. New Jersey* 46:87, 1949. 3. Cortese, J. T.: *Clin. Med.* 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: *M. Ann. District of Columbia* 17:389, 1948. 5. Hensel, H. A.: *Postgrad. Med.* 8:293, 1950. 6. Angelucci, H. M.: *Am. J. Obst. & Gynec.* 50:336, 1945. 7. Cicalese, G.: Personal communication. 8. Horoschak, A., and Horoschak, S.: *J. M. Soc. New Jersey* 43:92, 1946. 9. Crisp, W. E.: Personal communication. 10. Parks, J.: *M. Ann. District of Columbia* 12:175, 1943. 11. Kroger, W. S.: Personal communication. 12. Peikes, I. L.: In press.

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Just a "simple"
case of cystitis
may be the
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pyelonephritis¹—
or may actually be
the first evidence
of a pre-existing
pyelonephritic
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to ensure rapid control of infection
throughout the urogenital system

FIRST

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
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AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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Avoids unnecessarily diffuse or diverse drug action; effective in economical once-a-day dosage

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6-year record of successful use in daily practice; consistently favorable reports¹⁻¹⁰

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no known contraindications; free of hepatic, extensive, and hematologic hazards observed with phenothiazines

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(brand of procizine hydrochloride)

FORMERLY BONAMINE

SUPPLIED:

BONINE Tablets, scored, 25 mg.

BONINE Chewing Tablets, mint-flavored, 25 mg.

BONINE Elixir, cherry-flavored, ideal for children, 12.5 mg. per teaspoonful (5 cc.).

DOSEAGE: Adults, 25 to 50 mg. once a day.

BONINE REFERENCES:

1. Moyer, J. H.: M. Clin. North America, May 1957, p. 405.
2. Seidner, H. M.: J. Am. Med. Ass., 167, 10, 1957.
3. Charles, F. C.: J. Am. Med. Ass., 167, 10, 1957.
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10. Report of study by Navy, Navy Air Force Motion Sickness Team: J.N.A. 166:755, 1954.

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relaxes muscle tension

raises the pain threshold

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analexinTM

phenylamidol HCl

*a single chemical that is both a general non-narcotic
analgesic and an effective muscle relaxant*

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announcing a new class of drug

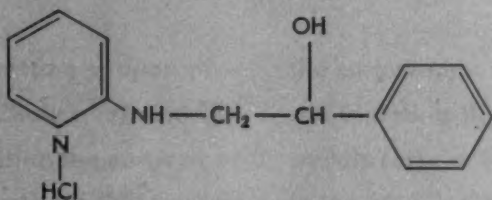
analexin



**therefore...in pain...
where pain makes tension
and tension makes pain...
analexin stops both effectively**

A Analgin is a new synthetic chemical (phenylamidol hydrochloride) that inherently possesses within one molecular structure two different pharmacologic actions: (1) *general analgesia*, by raising the pain threshold and thus decreasing the perception of pain, and (2) *muscle relaxation*, by selectively depressing subcortical, brain stem and spinal polysynaptic transmission (interneuronal blockade), abolishing abnormal muscle tone without impairing normal neuromuscular function.^{1,2}

A Although the analgesic potency of one tablet is clinically equivalent to one grain of codeine, Analgin is not narcotic or narcotic related. It is not habituating and tolerance to the drug has not been noted. Muscle relaxant action is comparable to the most potent muscle relaxants available for oral use. *The total effect is "analgomyrelaxation"—a new advance for the relief of pain.*



The full chemical name for phenylamidol is 2-(β hydroxyphenethylamino)-pyridine hydrochloride. It is unrelated to any currently available analgesic or muscle relaxant compound.^{3,4}

Meisler

analexin provides effective relief of the total pain experience...

⌘ The end result of pain, regardless of its origin, is discomfort or suffering paralleled by muscle tension. Thus muscle tension may play a fundamental role in the total pain experience even though it does not initiate the pain. Employment of a single agent that produces two distinct but associated physiologic responses has obvious advantages, for relief of the total pain experience is better accomplished by the integrated action of phenylramidol which acts on both pain centers and muscle to produce analgesia and relieve muscle tension simultaneously.

with remarkably few side effects

⌘ Side effects such as sedation, euphoria, mental confusion and depression, sometimes associated with inter-neuronal blocking and certain analgesic agents have not been noted with Analexin. Incidence of reactions is low and those reactions that occasionally occur (such as gastric irritation and pruritus) are of a mild and transient nature and do not limit therapy.⁵

Heieler

analexin



announcing a new class of drug

analexin


results with analexin in clinical trials

Batterman, Grossman and Mouratoff⁵ compared Analexin with aspirin, sodium salicylate and a placebo in a series of 195 patients with various painful conditions. The authors concluded:

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

"Phenylramidol (Analexin), with therapeutic doses is not only safe for chronic administration, but also to date we have noted no adverse effect upon the cardiovascular, gastrointestinal, respiratory, kidney, liver or central nervous systems."

Wainer⁶ reported a series of 200 cases treated with phenylramidol for various painful conditions. In fifty of these patients who had dysmenorrhea, he saw excellent results in 40, good results in 5 and poor results in 5. Further examination in 4 cases not responding revealed presence of organic pathology. A second group of 50 cases with headache and associated premenstrual tension responded with over-all excellent results. Wainer also reports the use of phenylramidol to replace codeine for postpartum pain and describes 100 cases wherein a combination of phenylramidol with aluminum aspirin (Analexin-AF) successfully replaced aspirin and codeine therapy.

Meisler

more results with analgin in clinical trials

⌘ In another series of dysmenorrhea cases, Bader⁷ compiled data on 20 employees of a telephone company who required ½ to 2 days off from work every month regardless of prior therapy employed. Satisfactory results were achieved in 15 out of 20 and a fair response in the remaining five. All were able to remain on the job although relief was not complete in the latter cases.

⌘ Bealer⁸ treated 32 patients with phenylramidol mostly for musculoskeletal disorders and had good or very good results in 15, fair results in 14 and poor or inconclusive results in 2 patients. Cohen⁹ used phenylramidol together with aspirin in 15 patients with such conditions as sciatic pain, osteoarthritis, anterior chest wall syndrome, etc. and got outstanding relief in 80 per cent. Gilbert¹⁰ reported that 15 patients with nonspecific headache had excellent relief in a matter of minutes with phenylramidol, and in 8 cases of dry socket pain Bruno¹¹ reports immediate relief in six cases and good results later in the other two after sockets were curetted under local anesthesia. Stern¹² reported on 40 ambulatory cases with a variety of painful conditions and saw good relief in 32 patients and poor in 8. Results were best in acute sacroiliac pain, myositis, muscle spasm, fractures, pleurisy and neuritis. Ten of 13 patients with osteoarthritis responded very well and are continuing on phenylramidol therapy.

Bealer

analgin



announcing a new class of drug

analexin

analexin (phenyramidol)

for relief of pain and muscle tension in:

low back pain
sprains and strains
myalgia
glass arm
wry neck
osteoarthritis
dysmenorrhea
tension headache
gout
postpartum pain
epigastric distress
(pylorospasms, gastritis, duodenal ulcer, cholecystitis)
genitourinary conditions
(premenstrual cramping or tension)
abdominal distress
(flatulence, colic)
toothache and dry socket pain

analexin-AF (phenyramidol with aluminum aspirin)

for relief of pain and muscle tension also
involving inflammatory processes and/or fever, as in:

arthritis
arthralgia
bursitis
tendinitis
myalgia of strain and tear
pre- and postoperative toothache

dosage:

analexin: for relieving pain and/or muscle tension, one or two tablets every 4 hours. In dysmenorrhea, two tablets initially then one tablet every 2 to 4 hours as needed.

analexin-AF: two tablets every 4 hours or as required.

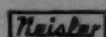
supply:

analexin tablets—Each tablet contains 200 mg. of phenyramidol HCl. Bottles of 100 tablets.

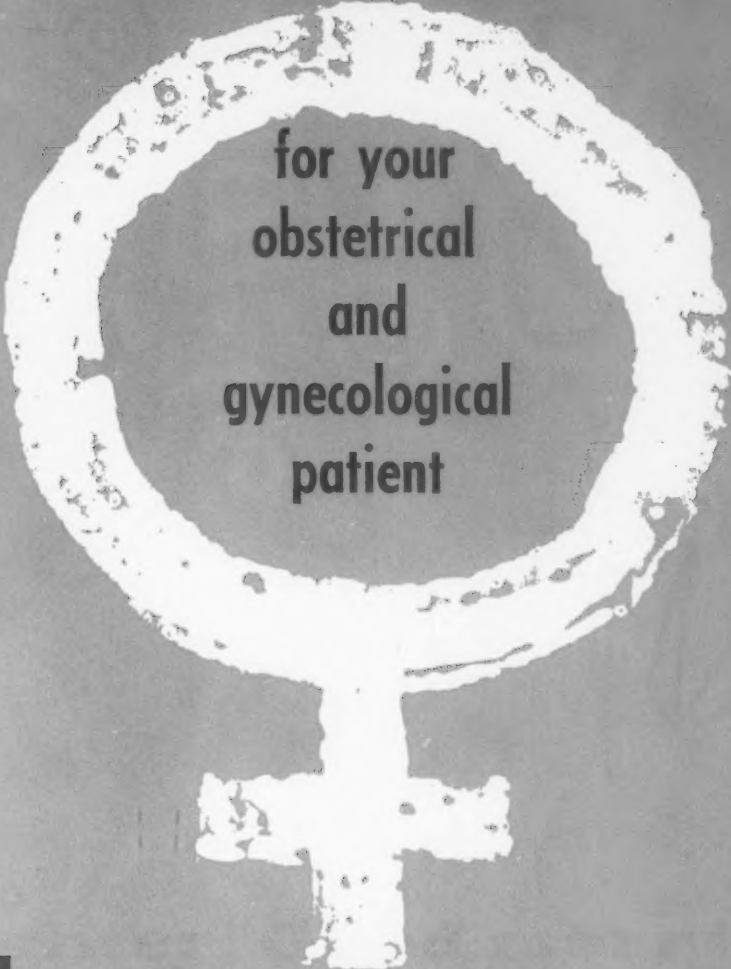
analexin-AF tablets — Each tablet contains 100 mg. of phenyramidol HCl and 300 mg. of aluminum aspirin. Bottles of 100 tablets.

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Clinical Reports cited above are in the files of the Medical Department, Irwin, Neisler & Co.



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obstetrical
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A single BACULIN vaginal tablet generally destroys the causes of vaginitis, namely Trichomonas Vaginalis, Candida Albicans, and non-specific organisms. Prescribe BACULIN vaginal tablets in your next case of non-venereal vaginitis.

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ACCIDENTS OF PREGNANCY CAN NOT BE CURED. THEY MUST BE PREVENTED.
desplex IS A CLINICALLY PROVED ANTIABORTIVE.

desplex, a unique combination of ultramicronized diethylstilbestrol and vitamins C, and B complex, was shown 96% effective in carrying 1200 difficult pregnancies to term.¹ For assurance of a successful pregnancy, prescribe desplex tablets. Now contains hesperidin complex.

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. . . SAFELY . . . EFFECTIVELY . . . ECONOMICALLY.

Just prescribe BANAUSEA tablets, one upon arising and one at bedtime. Turn your patients' blue mornings pink with BANAUSEA tablets.

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Reference: 1. Peña, E. F., Med. Times, 82-921, 1954.



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Double-strength capsules for maximum economy and convenience.

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(Marks, M. M.: Clin. Med. 4:151, 1967.)



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No complaints about

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Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

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For quick spray application. Available in 3 oz. prescription size, and 5.5 oz. and 11 oz. dispensers.

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For simple manual application. Available in 1 oz. tube w/applicator.

1. References on request.



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Many women don't know that a vinegar douche is as old-fashioned as the copper tub, a relic of an empiric age.¹ Acids actually make mucus discharge more tenacious. On the other hand, soaps and harsh alkali are irritating. A detergent douche — TRICHOTINE, the only major douche containing sodium lauryl sulfate — is the modern, more

efficient yet gentler vaginal irrigant.

The detergent action of TRICHOTINE assures greater penetration of viscid mucus, better dispersion of the healing medicaments on the mucosal surface, and more efficient removal of vaginal discharge.

If there is any doubt in your mind, compare TRICHOTINE with vinegar or any other

1. Goodman, L.S. and Gilman, A.: *The Pharmacologic Basis of Therapeutics*, MacMillan, 1955.



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solution in your office clean-up. You will see readily the advantages of TRICHOTINE. It will prove equally desirable for home douching.

The pH changes produced by any low pH douche last only a few minutes² and are of questionable value in healing.³ TRICHOTINE actually favors epithelial growth and

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375 Fairfield Avenue, Stamford, Connecticut

2. Karnaky, K.J.: J.A.M.A. 157:1155, 1955 (August)

3. Scheinberg et al: Surgery 24:972, 1948 (Dec.).



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makes the cancer patient more comfortable

- reduces impact of pain
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NIAMID lessens the need for narcotics in the depressed cancer patient and appears to potentiate pain-relieving agents. As pain is reduced and mental outlook improves, apprehension and depression are replaced by a brighter and more alert attitude, and appetite returns. The family, too, is cheered by the improvement in the patient's condition. On NIAMID therapy, patient care becomes noticeably less demanding.

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*the mood brightener
in cancer*



Science for the world's well-being™

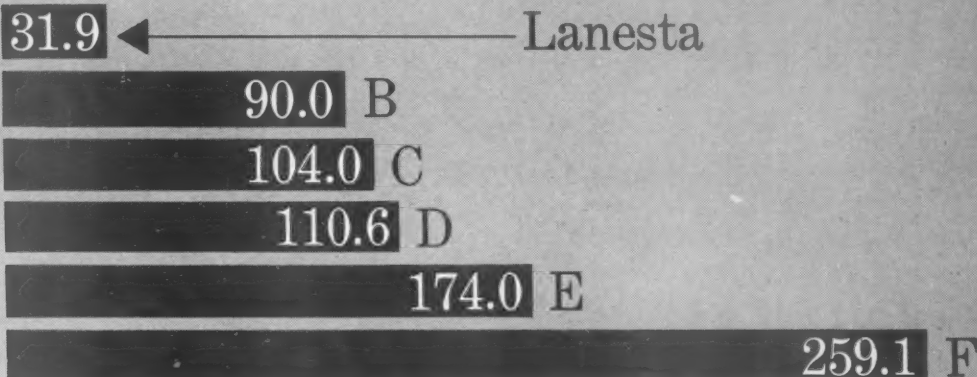


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speedier spermicidal action

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Mean Spermatocidal Time \pm S. E., Min.

Berberian, D. A., and Slighter, R. G.: J.A.M.A. 168:2257 (Dec. 27) 1958.

4 active agents provide speed and efficacy...

- 7-chloro-4-indanol, the new spermicide, rapidly and completely immobilizes sperm in concentrations as low as 1:4,000—yet is so mild that it may be used even in the presence of vaginal infection.
- 10% NaCl in ionic strength greatly accelerates spermicidal action.
- sodium lauryl sulfate acts as a dispersing agent and spermicidal detergent.
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Lanesta Gel® with diaphragm provides the most effective means of conception control. However, if a patient is unwilling or unable to use a diaphragm, Lanesta Gel provides faster spermicidal action—plus desirable occlusion at the cervical os when used alone.

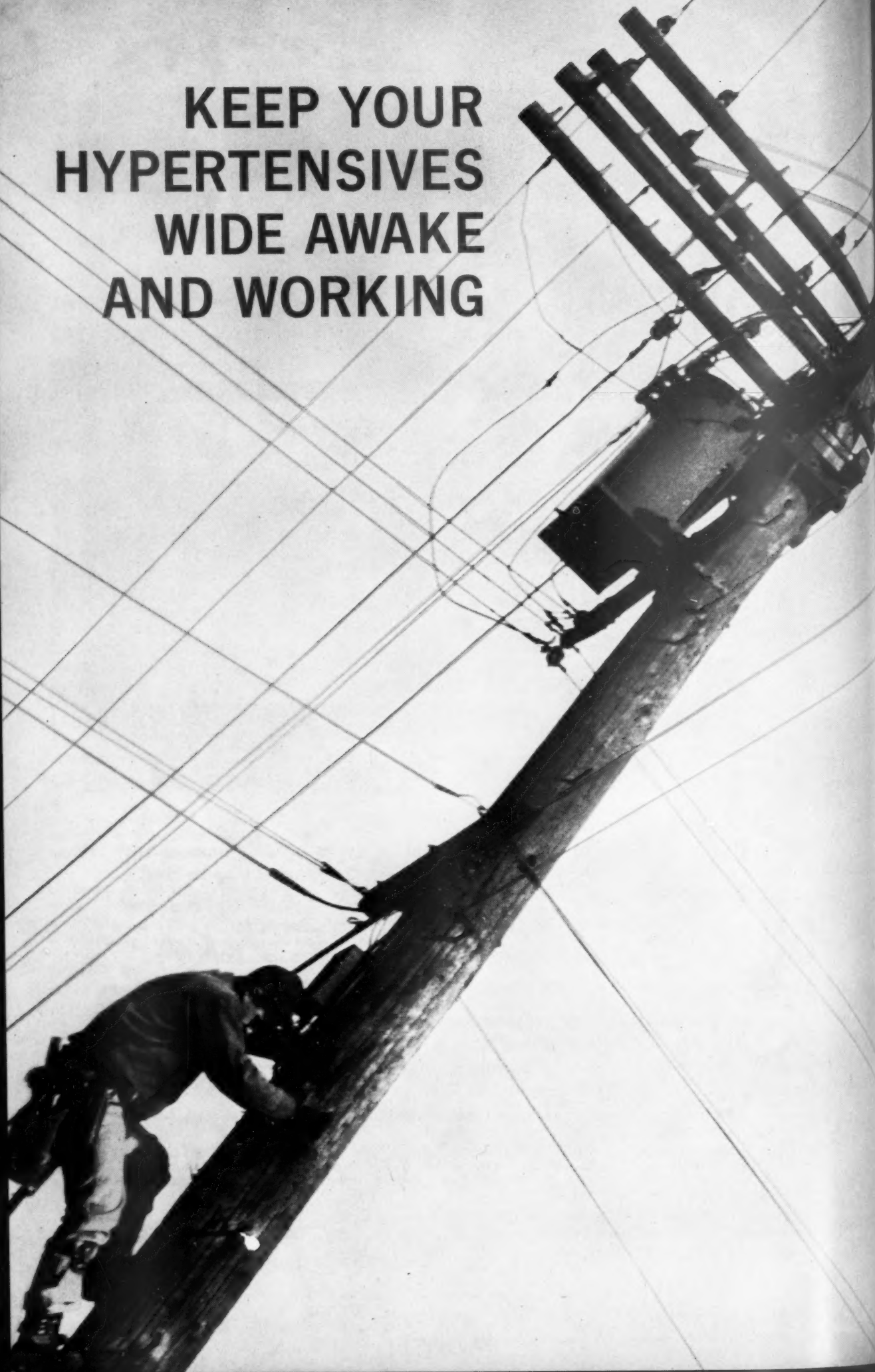
Supplied: Lanesta Exquiset (Physician's Prescription Package), 3 oz. tubes with applicator; 3 oz. refills. Available at all pharmacies.

References: 1. Berberian, D. A., and Slighter, R. G.: J.A.M.A. 168:2257 (Dec. 27) 1958. 2. Bailey, J. H.; Coulston, F., and Berberian, D. A.: J. Am. Pharm. A. (Sc. Ed.) 48:212 (April) 1959. 3. Gamble, C. J.: Am. Pract. & Digest Treat. 9:1818 (Nov.) 1958. 4. Berberian, D. A.; Coulston, F., and Slighter, R. G.: Toxicol. & Appl. Pharmacol. 1:366 (July) 1959. 5. Warner, M. P.: J. Am. M. Women's A. 14:412 (May) 1959.

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CONTAINING 25 mg. ORETIC & 0.25 mg. HARMONYL

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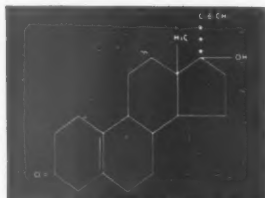
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GYNECOLOGY

Electrolyte in human myometrium

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ELECTROLYTE concentrations in human myometrium are of interest for several reasons. A theory concerning the action of ovarian hormones has been postulated,^{1, 2} in which it is suggested that progesterone alters the conduction of electrical activity and the distribution ratios of sodium and potassium across myometrium cell membranes. These effects are assumed to be interrelated and to explain, in part, the supposed quiescence of the uterus during the secretory stage of the menstrual cycle. However, there is much evi-

dence which does not confirm this supposed lack of contractile activity during the secretory phase in the human uterus,³ and no evidence that electrolyte concentrations in the human uterus are altered is given. The studies of electrolyte concentrations in animal uterine muscle are contradictory.^{4, 5}

Electrolytes in the pregnant myometrium are also of interest because it has been stated that pregnancy is associated with a significant loss of myometrial potassium and gain of sodium.⁶ The loss of potassium and gain of sodium was reported to be increased in labor—in particular, in prolonged ineffective labor. However, in a careful study,⁷ these findings were not confirmed, and the only significant change found in labor was in

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water concentration of the pregnant myometrium.

In addition, differences in electrolyte concentration might underlie the variation in mechanical activity which occurs both in vivo³ and in vitro.⁸⁻¹⁰ These variations include differences in activity of segments from various portions of the same uterus and differences in activity from similar portions of uteri studied at various stages of the menstrual cycle and in pregnancy.

Finally, changes in electrolyte composition in normal and in pathological conditions in the uterus may provide useful complementary objective data to that derived from histological and histochemical studies¹¹ and may aid in resolving differences.

Methods

Collection and handling of tissues. Tissues were removed at operation, either hysterectomy or cesarean section, and their wet weight determined immediately. They were dried for at least 5 days at 105° C. and reweighed to obtain the water content.

Analysis of tissue electrolyte. The dried tissues were ground, and aliquots were digested and the redissolved products of digestion analyzed for sodium and potassium content as previously described.^{5, 12-14} Chloride analysis of ground tissues was carried out in duplicate by an electrometric titration as suggested by Whittam.¹⁵ This method gives values identical with those previously obtained with use of an open Carius technique¹⁴ provided sufficiently large samples were used in the latter procedure. However, for the sake of uniformity, all chloride analyses are carried out with use of the electrometric method.

Classification of the tissues. Specimens of all uteri were examined by the same pathologist, and a statement was made as to the status of the endometrium. These classified the endometrium as being either in early, mid, or late proliferative stages or in early or late secretory stages. In addition, histories of the menstrual status were obtained in nearly every instance. The stages of the cycle were designated as follows:

early proliferative first to eighth day, mid-proliferative ninth to twelfth day, late proliferative fourteenth to sixteenth day, early secretory fifteenth to nineteenth day, late secretory nineteenth to thirty-second day. To obtain sufficient numbers for statistical purposes, the mid and late proliferative tissues were combined. In a number of instances, the statements of the pathologist were in disagreement with the menstrual history, and in such cases the slides were re-examined to resolve the discrepancies. Where such discrepancies could not be resolved, the data were not included in the control series. Dating of myometrium from cesarean sections was based on the clinical history.

Any tissues which, according to the pathological examination, were reported to contain multiple fibromyomas, adenomyosis, or carcinoma were excluded from the controls. In addition, tissues for which there was evidence of abnormal menstrual periods, of prolonged uterine bleeding, of luteal cysts, or of other hormonal dysfunctions were excluded. The control patients were operated on for procidentia, for endometriosis, or for pain from a single large fibroid. Of 64 uteri studied, 39 were finally selected for inclusion in the controls. It should be emphasized that this selection was in addition to that exercised initially in determining which uteri should be taken for analysis.

Expression of results. Because of the fact previously noted,^{5, 12} that the chloride space often exceeds the sodium space in uterine muscle, the conventional assumption that the chloride space is equivalent to the extracellular space is not tenable for these tissues. Therefore, the concentrations of sodium and potassium have been expressed relative to the fresh weight, to the dry weight, and to the tissue water. In addition, the volumes through which the sodium and chloride were distributed have been calculated to determine whether they provide any indication of changes in extracellular fluid volume. Variability of mean values has been indicated by the standard errors of the means.

Results

Data on electrolytes in the human myometrium are summarized in Table I. They are subdivided according to the site of origin of the piece of myometrium studied and according to their menstrual and reproductive status. Uteri from women many years past the menopause have been considered to provide data in which myometrium electrolyte concentrations were uninfluenced by ovarian hormones. These tissues were characterized by a high concentration of sodium and chloride and low concentration of potassium and water. Such concentrations of water and electrolytes are usually associated with the occurrence of a large proportion of acellular connective tissue.¹⁶ The composition of such tissues was the same, irrespective of whether the muscle analyzed was derived from the corpus or from the lower uterine segment; in other words, no chemical gradient was found.

Compared to tissues from women in the menopause, myometrium derived from uteri removed during the proliferative phase of the menstrual cycle contained less sodium and chloride but more potassium and water per unit of wet or dry mass. The increase in potassium concentration was relatively greater than that in tissue water concentration, so that the concentration of potassium per liter of tissue water was also elevated. The elevation in concentrations of potassium and water was greater in the upper and midsegments and least in the lower uterine segment, thus a gradient of concentration of these substances was found. There was a tendency for the sodium and chloride concentrations to be higher in the lower uterine segments than in the fundus. When the sodium concentrations were expressed relative to tissue water, this difference between the upper and lower portions of the corpus was accentuated because of the lower water concentrations in the lower uterine segments. In all segments of the myometrium, the sum of the concentrations of sodium and potassium in tissue water was decreased.

The sodium space was altered propor-

tionally more than the chloride space, when myometrium from the proliferative phase uteri was compared to that from postmenopausal uteri. This suggested that under the conditions prevailing in the myometrium during the proliferative phase, the sodium occupies spaces or binding sites from which chloride is excluded or that such are not present in the myometrium not exposed to ovarian hormones.

The differences observed between myometrium from proliferative and from postmenopausal uteri were most marked in tissues from the mid and late proliferative phases.

In myometria from uteri in the secretory stages of the menstrual cycle, some of the differences noted above tended to be reversed. Thus, the concentrations of sodium and chloride were somewhat increased, compared to muscle from uteri in the proliferative stage, though not significantly so in terms of wet or dry weight. The water concentrations were somewhat decreased as well, thus accentuating changes in the sodium concentrations expressed relative to tissue water. There was, however, no reduction in potassium concentrations. In fact, relative to dry weight and tissue water, the potassium concentration was sometimes significantly elevated in late secretory myometria.

In segments of myometrium taken from uteri at elective cesarean section, the concentrations of electrolyte and water in those from the corpus closely resembled the values found in late secretory myometrium, except that the water concentration was somewhat higher. In particular, there was no reduction in potassium concentrations irrespective of how this was expressed. In myometrium taken from the lower uterine segments at term, there were large differences from similar portions taken in the late secretory stage of the menstrual cycle. The concentrations of water, sodium, and chloride were much elevated. There were also changes in the relative values for the upper and lower uterine segments. This was the first instance in which the concentrations of water in the

Table I

	No.	Age	Analytical data*						Derived data*					
			Na _t	K _t	Cl _t	H ₂ O _t	Na _{DS}	K _{DS}	Na _{sp}	Cl _{sp}	Cl _{sp} - Na _{sp}	Na _{DS} ρ _t	K _{DS} ρ _t	Na + K _{DS} ρ _t
Upper														
Postmenopausal	5	63.4	86.0	36.8	68.4	803.0	436.6	187.0	614	622	8	107.1	45.8	152.9
Early proliferative	5	3.0	3.9	2.5	2.2	3.4	18.4	13.7	556	595	39	95.7	61.1	151.8
		39.8	77.8	49.7	65.5	813.2	418.2	266.6						
Mid and late proliferative	5	1.7	3.6	0.6	2.1	4.2	25.6	7.8	529	575	51	88.8	58.3	147.1
		38.6	73.3	48.1	63.3	825.2	419.8	274.8						
Early secretory	6	2.9	2.8	1.25	2.6	3.7	18.7	3.6	565	596	31	96.2	60.8	157.0
		42.8	79.1	50.0	65.6	822.2	447.2	281.7						
Late secretory	5	0.7	2.1	1.0	2.2	4.6	21.2	4.3	544	575	31	92.8	65.3	158.1
		40.4	76.2	53.6	63.3	821.0	426.8	299.0						
Pregnancy (near term)	5	1.1	3.05	2.7	2.1	2.5	22.4	13.0	565	577	12	95.7	65.0	160.7
		29.6	79.1	53.7	63.5	826.2	455.4	308.0						
Mid														
1			90.4	38.7	69.8	804.6	463.4	199.0	646	635	-11	112.4	48.1	160.5
			2.6	1.5	2.3	4.4	16.1	10.1						
2			80.1	48.6	64.4	815.6	434.8	263.2	572	585	13	98.2	59.6	157.8
			2.6	1.6	2.1	2.2	15.3	5.9						
3			72.4	47.6	63.1	823.2	411.4	269.0	517	574	57	87.9	57.8	145.7
			4.3	0.8	2.1	1.7	15.9	2.7						
4			75.8	50.1	63.3	816.8	415.2	272.8	541	575	34	92.8	61.3	154.1
			3.1	2.3	1.8	4.3	24.1	7.1						
5			81.3	52.2	65.3	819.0	451.4	305.4	581	594	13	99.3	67.4	166.7
			4.0	2.4	2.6	3.7	31.6	13.3						
Lower														
1			89.6	38.8	68.1	797.4	443.0	191.2	640	619	-21	112.4	48.7	161.1
			3.1	3.2	2.1	6.7	15.9	13.2						
2			82.4	42.5	70.0	803.8	420.0	216.2	589	636	47	102.5	52.9	155.4
			3.2	2.1	3.1	0.9	16.8	10.3						
3			78.7	44.7	64.9	812.8	420.6	240.4	562	590	28	96.8	55.5	152.3
			3.2	1.9	2.2	14.2	14.9	13.7						
4			81.0	46.6	63.5	808.2	425.0	244.4	578	577	-1	100.2	57.7	157.9
			2.5	2.8	1.75	6.3	22.6	17.5						
5			80.4	52.9	67.3	803.0	409.2	268.8	574	612	38	100.1	65.9	166.0
			1.0	2.2	2.1	3.6	12.2	8.1						
6	13	30.3	90.1	49.1	71.4	829.3	517.1	284.6	644	649	5	108.6	59.2	167.8
			3.4	1.9	1.7	1.9	17.7	13.8						

*In this and subsequent tables, the subscript *t* is used when values are expressed relative to tissue wet weight; *DS* is used when values are expressed relative to dry solids; *H₂O_t* is used when values are expressed relative to tissue water; *sp* refers to space.

lower uterine segment was as great as that in the fundus.

Uterine electrolytes in case of cesarean section after trial labor. Segments of the myometrium have been obtained in a few cases of uterine inertia. The analyses of two of these samples were so startlingly different as to warrant brief mention despite the careful studies made by Hawkins and Nixon⁷ on similar uteri. The relevant data are shown in Table II. In one instance concentrations of potassium and water were very low, whereas concentrations of sodium and chloride were high. Even here, the concentration of potassium was only slightly diminished relative to tissue water. This corresponds in history and in ion content to those reported by Hawkins and Nixon⁷ as "Delay late in labour." In the other instance, concentrations of potassium and water were much higher than the mean for the lower uterine segment of term while the concentration of sodium was lower. In this instance, the piece was derived from a postmature uterus which was relatively unresponsive and insensitive to Pitocin. Such results make it appear unlikely that one mechanism of effect relative to electrolyte distribution underlies uterine inertia. They support the view of Hawkins and Nixon⁷ that, when depletion of potassium occurs, it is an effect rather than a cause of prolonged labor.

Changes in electrolytes in the myometrium associated with uterine pathological conditions.

Adenomyosis. Analyses of human endometrium^{17, 18} suggest that it possesses a higher potassium concentration per kilogram than the myometrium and possibly a lower sodium concentration as well.¹² In the series of pathological specimens analyzed, several were reported to have adenomyosis (Table III) but in only one of these was the endometrial tissue present throughout the myometrium so that clear-cut alterations in the electrolyte pattern would be expected. In this instance (Case 50) there was an unusually high concentration of potassium, while the concentrations of sodium and chloride may have been slightly low but were not

remarkable for myometrium from a uterus in the late proliferative phase (according to the pathologist's report). In the other cases, the electrolyte composition of the myometria was to be expected from the histological classification. Before concluding that the myometrium in Case 50 showed altered composition of electrolyte because of widespread adenomyosis, it is necessary to note that it possessed a moderate number of fibromyomas. When the specimens for analysis were taken, these were avoided as far as was possible, but the composition of a large fibroid removed from a patient at cesarean section showed similar differences in composition of electrolyte (Table III) to that noted in the myometria with widespread adenomyosis. One difference was noted—the fibromyoma contained a very high concentration of chloride, as high as the sodium concentration. Whether or not this composition is characteristic of all fibroids and whether or not the composition of uterine fibroids is influenced by the ovarian hormones awaits further study. A final conclusion, therefore, cannot be drawn as to whether the extensive adenomyosis or the fibromyomas caused the altered composition of the myometrium in Case 50.

Luteal cysts. There were three instances in which luteal cysts were found. However, in only one of these was there histological evidence that it may have been functional. Unfortunately, in this instance, the operation was carried out on the eighteenth day of a 22 day cycle, presumably in the secretory phase. The composition of myometrial electrolyte was consistent with that of other specimens taken during the secretory phase. This analysis provided no information as to the effect of the production of abnormal progesterone on uterine myometrial electrolytes. The myometria from 2 patients with old hemorrhagic corpora luteal cysts and from 2 patients with old endometriomatous cysts were consistent in composition of electrolyte with expectations based upon their histological status.

Menorrhagia in older patients. In Table IV are summarized data on the composition

Table II. Myometrium from lower uterine segment after final labor

	Age	Na _t	K _t	Cl _t	H _t O _t	Na _{ds}	K _{ds}	Na _{sp}	Cl _{sp}	Cl _{sp} - Na _{sp}	Na _{H₂O_t}	K _{H₂O_t}	Na + K _{H₂O_t}
Case 1*	34	119.9	47.6	82.4	793	579	230	856	749	-107	151.2	60.0	211.2
Case 2†	21	76.4	63.6	71.7	830	450	375	546	652	106	92.0	76.6	168.6

*Primipara in labor 36 hours; head still not engaged because of orange-sized pelvic mass—ovarian tumor. Lower segment devitalized, i.e., deeply congested and thinned out at operation.

†Obese primipara. Estimated date of delivery was Dec. 2, 1957; last menstrual period Feb. 25, 1957; admitted to hospital Dec. 26, 1957. On December 27 pains started at 5 minute intervals; later became weak and irregular and stopped. Presenting part was high and cervix not effaced. A Pitocin drip (20 drops per minute in 5 per cent glucose containing 20 units per liter of Pitocin) was started at 10:30 A.M. December 29 and continued until 3:00 P.M. It caused strong, painful contractions at 3 minute intervals but cervical dilation was minimal. Fetal heart rate varied between 132 and 142 per minute. Emergency cesarean section was performed on December 30. The head not engaged, but engaging. "Cervix not ripe" was the comment of the obstetrician.

Table III. Adenomyosis and fibromyomas

Case No.	Adenomyosis	Age	Uterine weight (grams)	Fibromyomas	Endometrium	Na _t	K _t	Cl _t	H ₂ O _t	Na _{ds}	K _{ds}
28	Well defined but localized	37	290	Many (0.5 to 0.6 cm. in diameter), intramural, subserosal, and submucosal	Thin compressed; irregular; menorrhagia 1 month	77.2 85.8 73.6	33.8 32.8 25.6	64.4 68.4 64.7	798 785 776	382 343 328	167 131 114
57	Slight superficial	49	210	Moderate number (0.4 to 2.5 cm. in diameter), intramural and subserosal	Periods irregular; 2 years continuous bleeding for 2 weeks every period; moderately late proliferative	79.0 79.6 88.7	44.5 45.7 39.1	63.3 62.6 65.9	834 824 805	476 452 455	268 260 200
60	Scattered islands	48	95	None	Bleeding 6 months; late proliferative	91.2 75.2 81.1	44.5 46.2 44.1	70.5 70.5 62.5	822 816 791	512 409 388	250 251 211
50	Widespread	45	325	Moderate number (0.5 to 2.0 cm. in diameter), intramural and subserosal	Intermittent flow for 6 to 7 months; late proliferative	67.2 65.3 71.1	67.2 54.5 49.6	62.4 59.1 59.6	829 827 810	393 377 413	393 315 288
49	Scattered islands	41	210	Moderate number (0.2 to 3.5 cm. in diameter), intramural and subserosal	Periods normal but heavy flow; late secretory 21/28	71.1 73.7 77.2	53.4 51.2 52.1	59.5 63.9 71.1	818 816 796	394 400 379	293 278 256
Fibromyoma						69.8	63.6	69.3	812	371	320

of myometrium in patients upon whom hysterectomies were performed because of menorrhagia and who were older than 45 years of age. The first two (Cases 57 and 58) previously had had normal 28 day menstrual cycles but were now bleeding for a protracted period every 14 days. The clinical histories and the ages of the patients suggested that they were having anovulatory cycles. This led to the expectation that these myometria were exposed only to estrogen. Both the composition of electrolyte and the endometrial histological findings were compatible with that interpretation. The endometrium was classified as in the moderately late proliferative phase, and the water and electrolyte compositions were similar to those from myometria during the proliferative phase (Table I) but different from those from the myometria in either the postmenopausal or the secretory phase.

Data of the last 4 cases in Table IV were from women who had been bleeding continuously or intermittantly but irregularly for a protracted period. These women were older, except for the patient in Case 60, than those discussed previously.

In Cases 53, 60, and 61, both the histological analysis of the endometrium and the chemical analyses of the myometrium were compatible with the view that these uteri were exposed to estrogen but not progesterone. Histologically, the endometria were categorized as proliferative. The concentrations of potassium and water were higher than those of postmenopausal uteri, but usually not so high as in a normal proliferative phase (Table I). The concentrations of sodium and chloride, at least in Cases 60 and 61 were higher than in myometria in the proliferative phase and similar to those in menopause.

In Case 51, the endometrium was classified as postmenopausal hyperplastic. The myometrium was similar to that in Cases 60 and 61. This suggested that the myometrium and, presumably, the whole uterus were under the influence of estrogens, even though the histological findings in the endometrium demonstrated abnormality.

Comment

Comparison to other results. Few analyses have been made of electrolytes in the myometrium with use of modern techniques. In these we include our own recently reported measurements^{5, 12} and those of Hawkins and Nixon⁷ and Cort and Cort.⁶ Both Hawkins and Nixon and Cort and Cort use the chloride space or an arbitrary modification of this procedure to estimate the extracellular volume. Recently, in connection with analyses of the myometrium of a variety of species, some of the difficulties in accepting this procedure for uterine muscle have been set forth.⁵ No evidence for its validity for human uterus has yet been presented. Variations in procedures for taking and weighing tissues may have permitted varying degrees of tissue water loss in different studies. Therefore, comparisons have been based on the electrolyte concentrations per kilogram dry solids. The data of Hawkins and Nixon for nonpregnant myometrium consisted of analyses of 3 uteri in the proliferative and 2 in the secretory stage. Their data for sodium, chloride, and potassium per kilogram dry solids do not differ significantly from ours when they are compared to those of the samples taken from the upper segment in the late proliferative and early secretory phases. Similarly, their data for myometria samples at term do not differ significantly from the comparable data presented here. Similar comparisons to the data of Cort and Cort cannot be made because of their presentation of values for intracellular electrolytes per kilogram of fat-free dry solids without the necessary accompanying data which would enable calculation of the original analytical values. However, it appears unlikely that the values for potassium would be much altered by exclusion of extracellular potassium. In fact, the values of Cort and Cort for the intracellular concentration of potassium in nonpregnant myometria are higher than our own and those of Hawkins and Nixon. Further, the discrepancy would be decreased if they had included extracellular potassium as well. Thus, it appears likely that the hypothesis

of Cort and Cort that a loss of potassium from the myometrium takes place during pregnancy was based upon unusually high concentrations of potassium for their non-pregnant uteri. In addition, the myometrial concentrations of potassium reported by Cort and Cort at term are somewhat lower than those obtained by us and by Hawkins and Nixon. The values for intracellular sodium in pregnancy reported by Cort and Cort cannot be compared since the increased intracellular concentrations they obtained may have been calculated as a result of a decrease in chloride content as well as an increase in sodium content.

Pathological changes and uterine electrolytes. The data in Table III indicate that altered myometrial concentrations of electrolyte may accompany widespread adenomyosis and numerous fibromyomas. The concentration of potassium appears to be elevated and the concentration of sodium diminished in these conditions. The concentrations of chloride may be high relative to the concentrations of sodium in fibromyomas. If such alterations regularly accom-

pany these conditions, the occurrence of similar lesions might account for the values obtained by Cort and Cort in nonpregnant patients.

Analyses of myometria from older women with abnormal uterine bleeding (Table IV) suggested that these uteri were under hormonal influences similar to those which prevail in the early proliferative stage, i.e., estrogen stimulation. There was a tendency for the values to be intermediate between those obtained in tissues from normal proliferative phases and those obtained in true menopause. This may represent effects of subnormal estrogenic stimulation.

The data from pathological cases suggest that a careful study of the composition of electrolytes of a large number of specimens in such cases might provide new insight into the operative mechanisms. Correlation of such data with studies of plasma and urine levels of hormones and histochemical analysis of the endometrium should prove particularly rewarding.

The data from pathological uteri indicate the importance of excluding such material

Table IV

Case No.	Age	Uterine weight (grams)	Fibromyomas	Endometrium	Na _i	K _i	Cl _i	H ₂ O _i	Na _{DS}	K _{DS}
<i>Probable anovulatory cycles</i>										
57	49	210	Moderate number (0.4 to 2.5 cm.), intramural and subserosal	See Table III	79.0	44.5	63.3	834	476	268
					79.6	45.7	62.6	824	452	260
					88.7	39.1	65.9	805	455	200
58	48	105	Few (0.2 cm. in diameter), intramural	Now 2 weeks—bleeds 10 days; moderately late proliferative	76.0	45.3	66.9	826	437	260
					80.7	46.6	60.1	813	432	249
					86.1	29.6	73.9	794	418	144
<i>Menorrhagia and metrorrhagia</i>										
51	52	190	Many (1.0 to 3.0 cm. in diameter), intramural and subserosal	Postmenopausal; hyperplastic	71.9	36.8	57.3	826	413	212
					79.7	41.3	72.7	824	453	234
					78.1	40.3	64.0	810	411	212
53	52	150	4 or 5 (2.0 to 3.5 cm. in diameter), subserosal	Moderately late proliferative	72.2	50.8	61.6	811	382	269
					68.5	42.2	58.8	822	385	237
					80.5	43.3	64.0	821	450	242
60	48	95	None	Late proliferative	91.2	44.5	70.5	822	512	250
					75.2	46.2	70.5	816	409	250
					81.1	44.1	62.5	791	388	211
61	52	230	Many (1.5 to 6.0 cm. in diameter), intramural and subserosal	Moderately late proliferative	91.5	40.6	72.8	818	502	223
					87.2	37.4	71.7	818	479	205
					92.4	31.6	73.3	778	416	142

from analyses designed to study only physiological variation. We believe that we were substantially successful in excluding such material from our series at different stages of the menstrual cycle. These uteri were all derived from women approaching or in menopause, however, and it would be desirable to carry out similar studies on younger women (sexually immature and mature) to show that the aging process does not influence the results obtained.

Relation of the results to various hypotheses. These results provide no support for the hypothesis^{1, 2} that progesterone diminishes the potassium concentration of the uterine muscle cells. Thus, in the secretory phase and in pregnancy when progesterone should be acting, the concentration of potassium expressed in terms of fresh weight, dry weight, or tissue water, was at least as great as that in the proliferative phases when, presumably, only estrogen is acting. Furthermore, there was no suggestion that progesterone caused the intracellular phase to expand at the expense of the extracellular phase, since the sodium and chloride spaces were undiminished in myometria in the secretory phase and in pregnancy. Therefore, it is not possible to avoid the implications of these data by assuming a dilution of cellular potassium by the excessive entrance of water. The bulk of evidence from analyses of animal myometria^{5, 19} is in agreement with these findings. These data do not, however, rule out the possibility that very high local concentrations of progesterone produced by the placenta may alter the concentration in the overlying myometrium.

The electrolyte composition of the human myometrium provides little chemical basis for the claim that there is an antagonistic action of progesterone on the effects of estrogen on uterine contractility in the human.^{12, 20} There was a tendency for the sodium concentration to be increased in secretory and pregnant myometria compared to those in the late proliferative stage. There was also a tendency for the water concentration to be reduced in myometria during the secretory phase, so that the sodium con-

centration per liter of tissue water was elevated. This value was also high in myometria during pregnancy. The possibility exists that progesterone may antagonize the effects of estrogen to decrease sodium and increase the water concentration of the uterus. Studies of the composition of myometria taken after injection of these hormones would aid in elucidating this possibility.

These data, in agreement with those of Hawkins and Nixon provide no support for the view⁶ that at or near term there is depletion of potassium and gain in sodium from the muscle cells of the myometrium. Data from myometria taken at emergency cesarean sections reiterate the fact that failure of the function of the myometrium in labor may be due to more than one cause. Slight potassium depletion did accompany prolonged labor, ineffective because of disproportion, but it did not occur in one instance in which a postmature myometrium was found to be relatively unresponsive to Pitocin.²¹ Probably potassium depletion from the human myometrium occurs only during prolonged forceful contraction, as in other smooth muscle.^{7, 22}

These results provide further evidence for the existence of a chemical gradient from fundus to cervix which might influence uterine mechanical activity. Previous workers have shown that differences in mechanical activity occur both in the nonpregnant and in the pregnant state between the fundus and the isthmus, whether this activity is studied *in vivo*^{3, 23} or *in vitro*.⁸⁻¹⁰ Myometrium from both these regions has been shown to be histologically similar and to respond similarly to a stimulus such as pregnancy.^{24, 25} However, chemical differences have been found in the concentrations of physiologically significant components in these two portions of uterine muscle. For example, the fundus contains more contractile protein than the isthmus⁸ and more creatinine phosphate than the cervix.²⁶ The data of this study show clearly that the composition of electrolyte in the lower uterine segment differs from that of the upper and

midsegments. Thus, the nonpregnant myometrium from the fundus and midsegments contains more water, less solids per kilogram wet weight, and more potassium per kilogram dry solids. Concentrations of sodium and chloride are not significantly different in various portions of the myometrium. Such data imply that tissue water in the myometrium is replaced from the lower segment by solids with an electrolyte composition not unlike that of the extracellular fluid. In instances (i.e., proliferative phases) when potassium concentration per kilogram of weight is lower in the lower segment myometrium, the data are compatible with the suggestion that these solids have occupied space in the myometrium at the expense of intracellular material. Thus, these differences between the electrolyte compositions of the myometrium of the lower and other uterine segments could be explained if the lower segment contained a higher concentration of solid with the electrolyte composition of extracellular fluid (mainly Na and Cl) and either a lower concentration of cellular fluid (containing mainly K) in the proliferative myometrium or a lower concentration of extracellular fluid in the secretory myometrium. In pregnancy this chemical gradient partly disappears in that the water concentration of the lower segment has increased so that there is no difference in the water concentrations of myometrium from lower and upper segments. In these tissues, however, the concentrations of sodium and chloride of the lower myometrium of the lower uterine segments were larger, suggesting that the fluid taken up by the lower segment myometrium was extracellular (edema) fluid. Final interpretation of such data must remain speculative until correlation with other histological and chemical data is possible.

Summary

1. Analyses were carried out of the water, chloride, sodium, and potassium concentration of biopsy specimens of human myometrium. Comparisons were made between the values found in various stages of the

menstrual cycle, in menopause, in pregnancy, and in other various pathological states. Comparisons were also made of the values found in the various portions of the corpus (the upper, mid, and lower uterine segments).

2. In menopause, the myometrium was found to contain a low water concentration relative to other states and to have higher concentrations of those electrolytes (Na and Cl) which are present in high concentrations in the extracellular fluid. Correspondingly, it had lower concentrations of potassium, a component concentrated in cellular fluid.

3. In the proliferative and secretory stages of the menstrual cycle there was a higher concentration of water and of potassium in the myometrium than in menopause. The concentrations of sodium and of chloride tended to be lower; the water concentrations of the myometrium was highest in the mid and late proliferative phases. Potassium concentration was highest in the late secretory phase. Concentrations of sodium and chloride did not vary significantly during the cycle, but sodium concentration tended to be lower in the mid and late proliferative than in the secretory states.

4. In pregnancy, at term but before the onset of labor, the potassium and water concentrations of the myometrium are as high as or higher than in any stage of the menstrual cycle. The water concentration of the lower uterine segment is remarkably elevated compared to the nonpregnant state, and this change is accompanied by an increase in concentrations of sodium and of chloride.

5. The lower uterine segment was found to contain less water and sometimes less potassium than the upper and midsegments in all conditions studied except in pregnancy at term.

6. Various pathological myometria have been analyzed and the results discussed as illustrative of a possible insight to be gained by such analyses into mechanisms operating in uterine pathology.

7. Finally, the implications of these results with regard to current hypotheses as to the mechanism of action of ovarian

hormones and as to the differences in mechanical activity of various uterine segments have been discussed.

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The action of papain and bromelain on the uterus

Part IV. The effects of papain and bromelain on the internal os and uterine cornua

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THE activities of the uterine cornua have been observed by a number of investigators who have shown that their constriction may be initiated by tubal contraction. The uterine contraction then may or may not progress toward the cervix. The two horns may act independently of each other in some instances, but during labor in the human those contractions that are measurable in the cornua are usually productive of fundal, midportion, and lower segment contractions.^{10, 11} Since the cornual sphincter is an intimate part of the cornu,⁶ its activities would naturally be associated with any activities of the cornu as a whole.

The nervous supply of the uterus² is still not accurately defined. The association of a contraction pattern with dysmenorrhea has received much attention⁵ and relief of discomfort by denervation has been successful.^{1, 3} Conversely, the hyperirritability of the sphincter or tubes which might prevent fertilization has been relieved by some forms of denervation. Doyle⁴ found that denerva-

tion by resection of both sacro-uterine ligaments relieved tubal spasm. Kennedy⁹ postulated that the nervous center for the activities of the Fallopian tube and the internal os of the cervix was located in the intramural portion of the tube. Reynolds¹¹ showed that the uterine contractions of labor begin in the tube or in the cornua and progress toward the cervix.

Trauma, such as that produced by the conventional intrauterine cannula or dilatation of the cervix with the rubber olive on the cannula, can cause contraction of the cornual sphincter. Rough examination and anxiety increase the irritability of the cornua and the sphincter.

In the previous papers in this series,⁷ we have discussed the actions of papain and bromelain when they are used to irrigate the vagina and/or cervix. The changes were demonstrated by x-ray studies.

Part 1. The enzymes have excellent mucolytic properties and remove the thick, tenacious mucus from the cervical canal, resulting in much more dependable x-ray visualization.

Part 2. The enzymes have a marked relaxing effect on the cervix with relief of primary dysmenorrhea.

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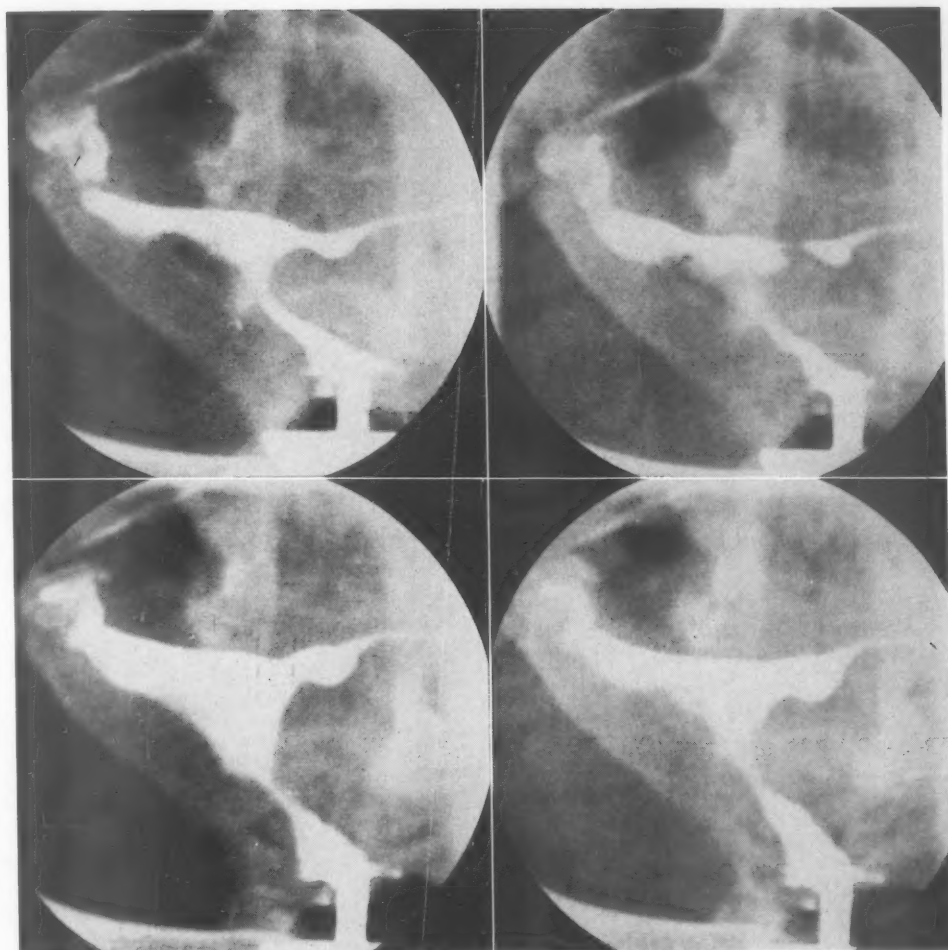


Fig. 1. Before papain.

Part 3. They may be used as a means of demonstrating physiological incompetence of the internal os.

In this paper we shall attempt to demonstrate the contraction patterns of the uterine cornu, the cornual sphincter, and the tube in association with the relaxation produced in the cervix.

The cervicohysterograms⁸ were done at or near ovulation as shown on a temperature chart. The examination was divided into 2 parts, one before irrigation with a solution of bromelain or papain, and the second part within 5 minutes after the irrigation. The fluoroscope was used and spot films were exposed at appropriate intervals. The cannulating instrument used was a revised Jarcho cannula.⁸

Fig. 1 is a normal uterus which shows the cornual sphincter in various stages of contraction and relaxation during the same examination. The medium* is out into both tubes.

Fig. 2 shows the same uterus after papain. The progressive contraction of both cornua beginning at the location of the tubal openings and progressing medially and toward the internal os is well shown. The tubal ostia are closed and there is no medium in the tubes.

This has been a consistent finding in 390 cases performed with this method. There

*Radiopaque medium used in these studies was Special Salpix supplied by the Ortho Pharmaceutical Corporation (each cubic centimeter contains 0.32 Gm. Sodium Acetate and 0.32 Gm. polyvinylpyrrolisone).

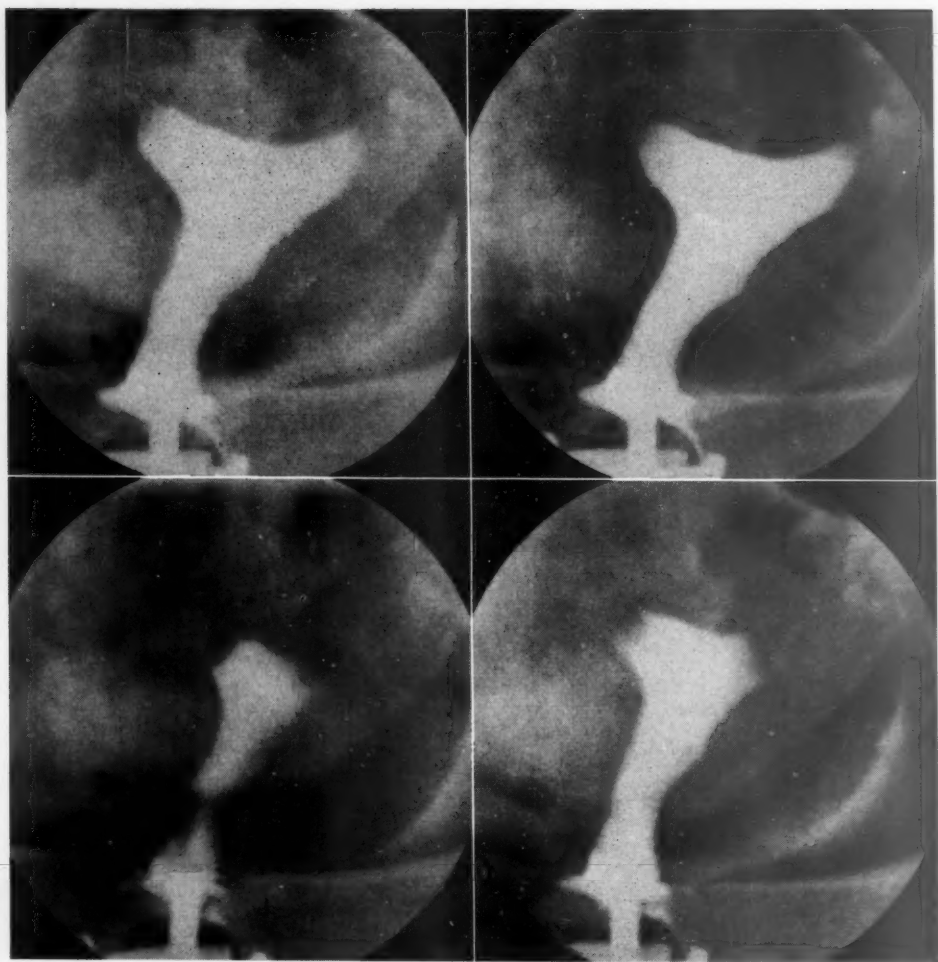


Fig. 2. After papain, showing the closed cornua.

has been a great deal of variation in the degree of contraction-relaxation in different patients. It would seem that there is a normal relationship between the state of dilatation of the cervix, the relaxation and contraction of the cornua, and the opening and closing of the cornual sphincters. Contraction of the cornual sphincter is associated with the relaxation and dilatation of the cervix.

Another patient who showed changes when treated with enzymes equally as great as those shown in the previous illustrations had endometriosis with implants on both sacro-uterine ligaments. At operation 2 cm. of each sacro-uterine ligament was resected and a fold of peritoneum interposed between the cut ends before they were reapproximated.

The postoperative film showed constant relaxation of the cervix which was unchanged by the enzyme. The cornua contracted after the enzyme as markedly as before, but the cornual sphincters remained partly open. This may be interpreted to mean that any spasm of the cervix, particularly the internal os, may be relieved by denervation, leaving the cervix relaxed at all times. This denervation does not interfere with the usual response of the cornua and its ability to contract. There is the suggestion that this denervation relaxes the cornual sphincters and decreases their response to the enzymes.

An attempt was then made to demonstrate that the area of the internal os was the initiating or trigger area in the enzyme response. The above patient was used. The

area of the internal os was exposed with a long nasal speculum and injected with 1 per cent Xylocaine and the same set of hystero-graphic studies repeated. The findings were as before. The cornua contracted but there was no change in the caliber of the cervix and the tubal ostia remained patent. The reaction to the enzyme solution was unchanged by the anesthetic agent. This would indicate that some area other than the internal os initiates the response usually seen in the cornual area excluding the sphincter. The receptor area may be the external os, the vagina, or intervening portions of the lower generative tract.

The probability is that the contraction-relaxation changes in response to enzymes are a normal physiological phenomenon. Since the x-ray studies have all been done at or near ovulation, these changes might represent the potential response to enzymes in male semen. One patient, who showed the typical pattern at ovulation in one cycle, was studied again at her next ovulation

with use of her husband's semen instead of the usual enzyme solution. The same changes were demonstrated as with enzymatic application. The cervix relaxed to the same degree that it did with enzymes, and the cornua contracted as before. The similarity of action of semen and these enzymes is most striking. Its significance can be clarified only after much more investigation of the various enzymes of semen, their separation and identification, and determination of their actions. Whether or not this response is essential to fertility may be answered by more study. The lack of essential enzymes in the semen of the males of infertile couples might be entertained as a cause.

The method of action of the enzymes is unknown. Apparently none of them have any demonstrable effect when taken orally. Still other routes of administration (besides instillation) have not been attempted. A great deal more study of the subject would seem to be indicated.

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Bacterial flora in vaginitis

A study before and after treatment with pure cultures of Döderlein bacillus

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IN 1892, Döderlein¹ discovered the vaginal bacillus in his study of puerperal sepsis. Later, however, the clinical importance of the bacillus of Döderlein in patients with vaginitis was demonstrated by Schröder.² After studying the vaginal flora of 288 non-pregnant women, he was able to divide his cases into 3 grades. Grade I, 40 per cent of the cases, had only the gram-positive vaginal bacillus. The vaginal secretions in these patients were always acid, and on examination of the vaginal wet smears only epithelial cells were found. In Grade II, 19 per cent of the cases, a mixed flora of Döderlein bacillus and various other organisms was found. In Grade III, 42 per cent of the cases, Döderlein bacillus was absent and there was a preponderance of micrococci, diphtheroids, and streptococci, and most of these cases had an alkaline discharge with many pus cells.

The fact that Grade I is consistently associated with normalcy of the vagina has been further established recently by the careful study of Lock and associates.³ They investigated the vaginal flora of 75 student nurses who were unmarried, between the ages of 17 and 25, and apparently without significant gynecological disease. By combining evidence from both cultures and smears, they found Döderlein bacillus in 100 per cent of their cases. By culture alone it was found in 83 per cent. A pure growth of Döderlein bacillus, or Grade I, occurred

in 49 per cent, and in these patients the pH of the vaginal secretion was always 4.5.

Because of these findings, it is not surprising that attempts have been made to restore the vaginal flora to normal by application of biological preparations. Löser,⁴ in 1920, used a lactobacillus preparation, while, in 1933, Orlowa⁵ claimed success with a culture of *Bacillus bulgaricus* in skim milk. In this country, Mohler and Brown⁶ treated 21 patients with severe vaginitis with only pure cultures of Döderlein bacillus. Six of their patients who were adequately followed were completely cured.

There has been renewed interest in this problem recently in Europe. Godinho de Oliveira,⁷ in a study of 49 cases of vaginitis treated only with daily applications of a pure culture of Döderlein bacillus, reported immediate relief of symptoms, a replacement of staphylococcus, diplococcus, streptococcus, and other bacteria with the Döderlein bacillus, and a shift in vaginal pH from 5.0 or 6.0 to as low as 4.0. Similar results with a lyophilized culture of Döderlein bacillus have been reported by Rindi.⁸

Methods and Material

Among several vaginal cultures taken from normal women, one from a 16-year-old girl grew out a pure strain of Döderlein bacillus. This strain grew best in the culture media and was found to persist better than the other strains when implanted into a recipient vagina. In this study it was called

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M-1. These Döderlein bacilli were cultured on peptonized milk fortified with V-8 vegetable juice, were incubated at 35° C., and were transferred to new media every 48 hours to maintain growth. Otherwise, excessive lactic acid formed which reduced further bacterial multiplication.

For clinical use, cultures grown in screw-capped bottles were centrifuged, the supernatant was decanted off, and the bacteria resuspended in 7 ml. of sterile skim milk. Control counts were made with bacteriotrypsin digest agar, and the number of Döderlein bacilli was maintained at approximately 1,000,000 per milliliter. These culture tubes were refrigerated until used. Batches were kept small enough to supply only 3 to 4 days of therapy.

Three methods of laboratory study were used in diagnosis and evaluation of therapy. They were wet smears, Gram-stained slides and agar plates. Wet smears were prepared by adding a drop of physiological saline to a drop of vaginal secretion taken from the upper third of the vagina with a wooden applicator after a vaginal speculum had been fully inserted. The preparation was mixed, covered with a coverslip, and examined immediately under $\times 450$ magnification. A sterile cotton-tipped applicator was used to collect material similarly for culture and Gram-stained smears. For culture, Petri dishes containing bacteriotrypsin digest agar were used. These were inoculated immediately, streaked for isolation, and incubated at 35° C. for 48 hours under increased carbon dioxide tension. To accomplish this, most of the air in the closed culture plate containers was replaced with pure carbon dioxide from a cylinder. When identified on the agar plates, the Döderlein bacillus colonies were 1 to 2 mm. in diameter, colorless, translucent, slightly raised, and showed a very characteristic roughness or "cording." Gram stains of these colonies always revealed long, pleomorphic Gram-indifferent rods. Likewise, other bacteria were identified by colony and microscopic morphology. Throughout the study the Kopeloff-Beerman modification of the Gram

stain was used. This modification utilizes an alkaline stain and an alkaline mordant.

In part of the study, a lyophilized preparation of the original M-1 strain of Döderlein bacillus was used instead of the skim-milk form. In the process of lyophilization, bacterial suspensions in sterile fat-free milk were prepared in 30 ml. quantities on a small laboratory freeze-drying unit. The bottles were shell frozen in a CO₂ ice-acetone bath and immediately placed under high vacuum. After drying was complete the vials were sealed. Control counts after reconstitution of this material were performed which indicated nearly complete viability of the original Döderlein bacilli.

Clinical study

The experimental group consisted of 165 patients with vaginitis seen in the private gynecological practice of one of the authors during the year 1958.

The study was divided into the first half of 1958, Plan A, and the last half, Plan B. In Plan A, at each office visit, besides the usual gynecological history, physical and pelvic examination, wet smears, slides for Gram stain, and agar plates for culture were taken. With the speculum still in place, the entire contents of a culture tube, approximately 7 million Döderlein bacilli, were poured into the vagina. An ordinary tampon was inserted and when the liquid was absorbed, the speculum was removed, leaving the tampon in place. The patient was instructed to remove it 5 to 6 hours later.

In Plan B, Gram-stained slides and wet preparations were relied upon to indicate the presence of Döderlein bacillus and to estimate their proportion in relation to other bacteria. Agar plates and colony identification were not used. Also, in the treatment of this group of patients, the lyophilized preparations were used instead of the earlier skim milk. The dry powder in the vials was reconstituted with 5 per cent glucose in water and 5 ml. of the preparation was used for each treatment. Again, the solution was instilled into the vagina with a syringe and held in place with a tampon.

The 135 patients in Plan A were seen at 540 office visits. To identify this group further, the average age was 33.5. Ten were single, 9 divorced, and the remainder, 115 married. Of these patients, 111 had been under periodic observation for an average of 15 months prior, during, and after the study. During the 6 months of the Plan A investigation, 89 patients were carefully observed an average of 2.6 months. These patients were further divided into groups: controls, pregnant, adequately, and initially studied cases. The first two groups are self-explanatory. "Initially studied" means that a diagnosis as to the cause of the vaginitis was made by cultures and smears, but these patients received only one or two applications of Döderlein bacillus and were not followed over a long enough period to evaluate what effect these few treatments might have. The "adequately studied" cases were treated, studied, and followed over a sufficient time so that the results of therapy could be determined. In Plan A, 96 patients were given 380 separate vaginal applications of the skim-milk Döderlein bacillus preparation. In 106 patients, 228 wet-mount slides were studied and in the entire group of 134 patients, 479 Gram-stained smears and 479 agar plates were studied.

The 69 patients in Plan B were treated with 124 vaginal applications of the reconstituted lyophilized Döderlein preparation. At each office visit Gram-stained smears and wet mount slides were examined.

In order to group and compare patients, it was necessary to classify them into one of 4 grades dependent upon the vaginal population of the Döderlein bacillus. This was done before, during, and after therapy, and was determined by agar-plate cultures in Plan A and by Gram-stained slides in Plan B. The cases were easily divisible into 4 grades. These were: Grade I, a pure growth of Döderlein bacillus by culture; Grade II, a predominate growth of Döderlein bacillus with only a rare colony of other organisms; Grade III, a mixture of organisms with Döderlein bacillus present; and Grade IV, any of the organisms commonly found in the vagina, but a complete absence of the Döderlein bacillus.

Actually, this classification was the same as the original Schröder, except that Schröder Grade II has been divided into Grades II and III. Grade I is the same as Schröder Grade I and Grade III of Schröder is identical with Grade IV in this study. The less quantitative and objective aspects of each grade were studied but were not used in the statistical part of this report. Thus, in Grade I there was usually no discharge, the vaginal secretions were acid, and on microscopic examination there were only epithelial cells and Döderlein bacilli. On the other end of the spectrum, Grade IV, there was often discharge and annoying symptoms, and the vaginal secretion was neutral or alkaline. On microscopic examination one would find pus cells and a variety of bacteria. Frequently these patients had yeast,

Table I. Presence of Döderlein bacillus as determined by vaginal culture in 124 cases of vaginitis

Cases	Per cent of cases		
	Grades I, II, III (with Döderlein)	Grade IV (without Döderlein)	Grade I (pure Döderlein)
75 normal unmarried young adults ³	83	4	49
15 normal controls (this study)	73	27	20
9 pregnant	56	44	22
44 monilia vaginitis	32	68	6
47 nonspecific vaginitis	19	81	2
17 trichomonas vaginitis	0	100	0
7 trichomonas and monilia vaginitis	0	100	0

Trichomonas vaginalis, or *Hemophilis vaginalis* present, but Döderlein bacilli were absent. Grades II and III were found in more of the normal patients.

Results

The premise of this study is that normally the Döderlein bacillus should be present in the vagina to the exclusion of almost all other bacteria and all pathogenic agents.

Referring again to the work of Lock and associates,⁸ Döderlein bacillus was found in 83 per cent of normal young unmarried women when the vaginal secretions were cultured. In the present study, by culture alone, Döderlein bacillus was found in 73 per cent of the 15 nonpregnant controls and in 56 per cent of 9 pregnant patients. In 44 patients with monilia vaginitis, 32 per cent had Döderlein bacillus, but it was found in only 19 per cent of the 47 patients with non-specific vaginitis. Döderlein bacillus was not isolated from any of the 11 patients with trichomonas or the 7 patients who had both monilia and trichomonas in the vagina. These results have been presented graphically in Table I. It emphasizes the correlation of absence of Döderlein bacillus and increasing severity of the infection. Another correlation was found when the incidence of Grade I was compared (Table I). Thus, 49 per cent of Lock's normal controls had a pure growth of Döderlein bacillus while in the married controls of this study a pure growth was found in 20 per cent. Among the cases of vaginitis there was a marked reduction in the incidence of Grade I cases. These were as follows: monilia vaginitis, 6 per cent; nonspecific vaginitis, 2 per cent; trichomonas, 0 per cent; and trichomonas combined with monilia, 0 per cent.

In Plan A, because of the culture methods used, *H. vaginalis* was not found; however, in both Plan A and Plan B, several patients who had the typical "clue-cells" as found by Gardner and Dukes⁹ and collaborated by Brewer and associates,¹⁰ when culture was done by the method used in this study, did not have Döderlein bacillus. These cases of suspected *H. vaginalis* were included among

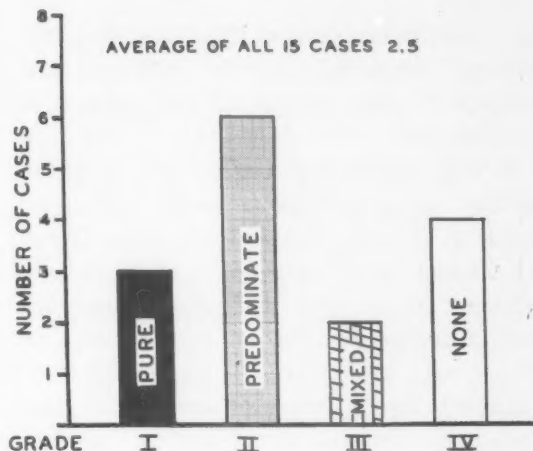


Fig. 1. Döderlein bacillus in 15 normal controls.

the cases of nonspecific vaginitis. A further study of the specific problem of *H. vaginalis* in relation to Döderlein bacillus will be published later.

To facilitate compilation and comparison of the data resulting from this study, the various grades were given an identical numerical rating. Thus Grade I was equivalent to 1, Grade II, 2, Grade III, 3, and Grade IV, 4. Thereby, an average grade for a group of cases could be found after each case had been allotted the proper rating. For example, the average grade of the 15 controls was 2.5 or halfway between Grade II and Grade III, indicating the presence of Döderlein bacilli in most cases (Fig. 1). An average of the 9 pregnant cases was 2.9, close to Grade III. The 47 cases of non-specific vaginitis averaged 3.7, the 44 cases of yeast vaginitis, 3.9, the 17 cases of trichomonas, 4, and the 7 cases with both yeast and trichomonas, 4. Thus, all of the cases of vaginitis averaged 4 or Grade IV. When patients with Grade IV flora were treated with the Döderlein bacillus preparation, the studies made on the next visit would indicate if there had been a change. Thus, for example, if 5 cases of nonspecific vaginitis were all Grade IV initially but after one treatment with Döderlein bacillus became Grade I, the average grade for these cases would be 1 and the result could be so graphed as a change in grade from 4 to 1. In Figs. 2 and 3, the actual changes in aver-

age grade in the cases of this study were represented graphically in this manner. The number of cases comprising each sum is in parentheses.

In Fig. 1, the controls are presented according to grade and number of cases: Grade I, 3 cases; Grade II, 6 cases; Grade III, 2 cases; and Grade IV, 4 cases. In percentages, 73 per cent of the control patients had Döderlein bacillus on culture, and, in 20 per cent, a pure growth was found.

Among the 9 pregnant patients, 4 had nonspecific vaginitis, 4 had monilia vaginitis, and one had trichomonas and monilia vaginitis. Of the 5 cases of monilia and trichomonas, 4 were Grade IV and 1, Grade III. Of the 4 cases of nonspecific vaginitis, 2 were Grade I, 1 was Grade II, and 1, Grade III. As an entire group Döderlein bacillus was found in 56 per cent on culture; in 44 per cent there was none, while in 22 per cent Döderlein was present in pure culture (Table I).

In this study there were 44 patients with monilia vaginitis. The grade average of these patients initially was 3.9. There was one case in Grade I, 2 in Grade II, 11 in Grade III, and 30 in Grade IV. In per-

centages, 32 per cent had Döderlein bacillus, and of these only 2.3 per cent had a pure growth, while no Döderlein bacillus was found in 68 per cent (Table I).

Of the 44 cases of monilia vaginitis 25 were studied adequately in respect to therapy with Döderlein bacillus. These cases have been represented graphically in Fig. 2. Among these patients 88 per cent were completely cured, but in 3, or 12 per cent, there was a persistent positive culture for yeast (Table II). Two of these symptomatically cured patients were treated 3 times and one 4 times with applications of Döderlein bacillus. Most likely with further treatment the cultures would have become negative. All 25 of these patients were treated with pure cultures of Döderlein bacillus at each visit. Besides, they were instructed to use Mycostatin vaginal suppositories (Squibb) twice each day for the first week of therapy. At the end of that time, as seen in Fig. 2, after the initial application of Döderlein bacillus, the grade average of the 25 cases was 2.3, indicating a predominate growth of Döderlein bacillus. Further treatments were with Döderlein bacillus only. After the third treatment most patients were com-

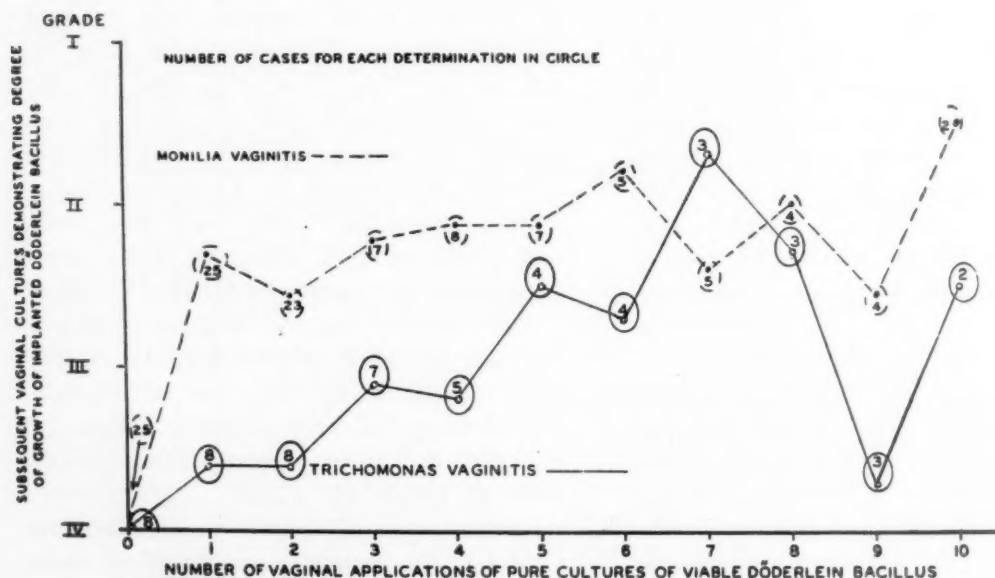


Fig. 2. Results of therapy with application of pure cultures of Döderlein bacillus in 25 patients with monilia vaginitis and in 8 patients with trichomonas vaginitis who were "adequately studied."

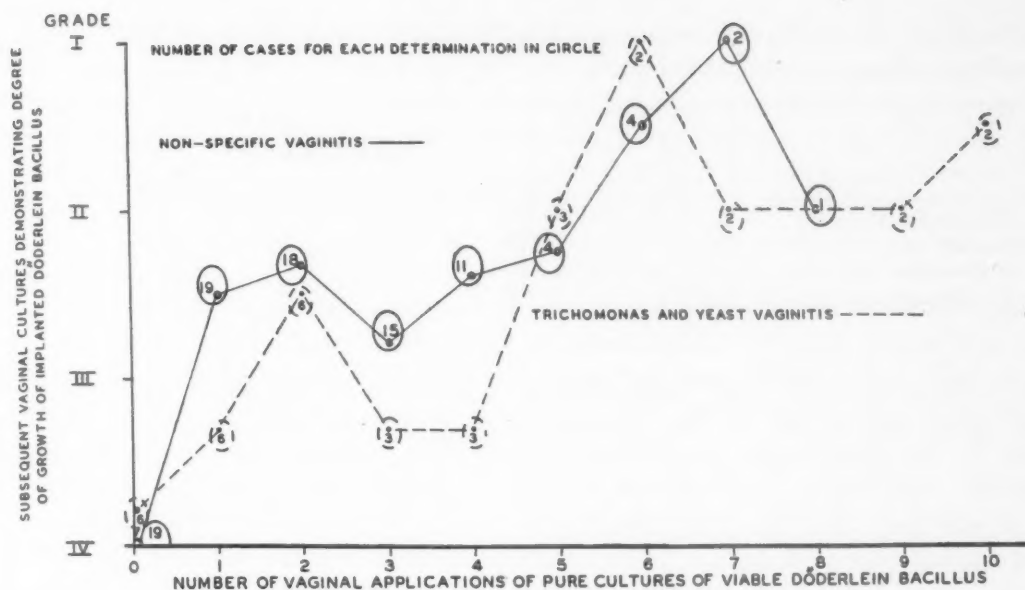


Fig. 3. Results of therapy with application of pure cultures of Döderlein bacillus in 19 patients with nonspecific vaginitis and in 6 patients with combined trichomonas and yeast vaginitis who were "adequately studied."

pletely free of symptoms, their cultures were negative for yeast, and there was a predominate growth of Döderlein bacillus. Only 7 patients continued to the end of the study although free of symptoms. In this smaller group with further Döderlein bacillus treatments the degree of purity of Döderlein bacillus in the vagina increased further to a final numerical grade of 1.5.

The 47 cases of nonspecific vaginitis were divided into grades and cases as follows: Grade I, 3; Grade II, 1; Grade III, 5; and Grade IV, 38. The grade average for the entire 47 cases before therapy was 3.7. From another point of view, 81 per cent of the patients had no Döderlein bacillus on culture and of the 19 per cent who did, only 6 per cent had a pure growth or Grade I (Table I).

Of these patients, 19 were in the adequately studied group and among these before onset of therapy the division into grades was as follows: Grade I, 0; Grade II, 0; Grade III, 1; Grade IV, 18; or an average of 4. Thus, as represented in Fig. 3, after one treatment with Döderlein bacillus, one week later the average grade was

between II and III, or 2.5, and with subsequent treatments a greater preponderance of Döderlein bacillus was obtained. All of these patients were treated with *only* cultures of Döderlein bacillus. Treatments were at first at weekly intervals and then at 2 week and finally at monthly intervals. As seen in Fig. 2, in spite of the long period of the study, once introduced into the vagina, the Döderlein bacilli persist. Of course, as the patients were relieved of symptoms, fewer returned for further treatments. Of these 19 patients (Table II), 18, or 95 per cent, were completely cured. One had no symptoms but, in spite of 4 applications of Döderlein bacillus, on subsequent examination Döderlein bacillus could not be recovered. This patient was, therefore, considered only symptomatically cured.

The 17 cases of trichomonas vaginitis were all initially Grade IV. Thus, Döderlein bacillus was absent in all. Of the 8 cases studied adequately all were cured except one which was a failure; in 2 of the cured patients there was a recurrence of the trichomonas vaginitis weeks later.

These patients were treated with Döder-

Table II. Results of therapy with vaginal application of pure cultures of Döderlein bacillus in 58 adequately studied cases

Cases	Per cent of cases			
	Cured	Symptomatic cure	Failure	Recurrence
19 nonspecific vaginitis	95	5	0	0
25 monilia vaginitis	88	12	0	0
8 trichomonas vaginitis	87	0	13	25
6 trichomonas and monilia vaginitis	100	0	0	0

lein bacillus at each visit. Each patient was given initially one or two treatments with a cinquarsen compound (No. 21 Powdex, Greenspun Laboratories), and those with persistent cases were given Devegán vaginal tablets (Winthrop) to use twice a day for one week at home. With Döderlein bacillus treatments first at weekly and then monthly intervals, there was a slow development of residual Döderlein growth, but, as the trichomonas disappeared and the use of arsenicals and Devegán finished, Döderlein bacilli became prominent and most cases became Grade II (Fig. 2). The low average toward the end of the study was due to the one failure. In this patient Döderlein bacilli would not grow. There was also a return to Grade IV of a case that was "cured" but later recurred. Of these 8 cases, 7 were cured, 87 per cent; one was a failure, 13 per cent; and in 2, reinfection or recurrence occurred later, 25 per cent (Table I).

Seven patients had a combined vaginitis due to trichomonas and monilia. All these cases were Grade IV and, therefore, there was no Döderlein bacillus in the vagina initially. Six were adequately studied and treated. Powdex, Mycostatin vaginal suppositories, and Döderlein bacilli were used initially and then only Döderlein. Surprisingly, all of these patients were cured and a Grade II vaginal flora obtained (Table I and Fig. 3). There were no recurrences.

The plan B cases demonstrated that the lyophilized Döderlein bacillus preparation gave similar results in subsequent growth of Döderlein bacillus and in therapy in the treatment of the various types of vaginitis

as did the skim-milk preparation used in Plan A. It had the advantages of more uniform bacterial count, preservation without refrigeration, permanence without deterioration, accessibility, and ease of use. A critical analysis of these cases is not presented because cultures were not taken in this group and Gram smears and study of wet-mount slides were not considered sufficiently reliable to warrant conclusions based upon these studies alone.

Comment

When cultural methods are used which are especially designed to favor growth of Döderlein bacillus, positive cultures will be found in a high percentage of normal women. But the normal vaginal flora, that is, a pure or predominate growth of Döderlein bacillus, can be easily altered since this microorganism is sensitive to many antibiotics¹¹ used today. Then, too, the effect of contraceptive jellies, douches, and various vaginal medicines upon the normal vaginal flora needs study in light of this investigation. Certainly, from this study there is one positive conclusion, that is, there is a lack of Döderlein bacillus in most patients with vaginitis. Does the Döderlein bacillus disappear first and then the vagina become invaded with pathogenic organism? Or do the pathogens, by their invasion, destroy the Döderlein bacillus? Which is the cart and which is the horse is theoretical, but, either way, re-establishment of normal flora should be strived for in these women.

Our findings are not in agreement with recent articles which report no significant alteration in the vaginal flora of "abnormal"

as compared to "normal" patients.¹² Even in trichomonas, Lash¹³ reports a similar incidence of Döderlein bacillus in controls and in infected patients. However, Weinstein and co-workers¹⁴ and Freed¹⁵ are in complete agreement with our findings. They have also found that Döderlein bacillus is rarely, if ever, present in patients with trichomonas vaginitis.

The increasing incidence of monilia vaginitis following systemic and vaginal therapy with some antibiotics is widely recognized. In these cases, possibly, the destruction of the Döderlein bacillus by the antibiotic may be important. The upset in the vaginal flora balance certainly allows yeast cells to multiply. To counteract these changes rational therapy requires prophylactic and therapeutic suppression of the monilia and preservation or restoration of the normal vaginal flora by vaginal treatments with pure cultures of Döderlein bacillus.

Unfortunately, the diagnosis of nonspecific vaginitis has become one of exclusion. That is, if a case of vaginitis is not due to monilia or trichomonas, it is considered nonspecific. The recent elucidation that some of these cases are due to *H. vaginalis* is a step in the right direction. With further study possibly a specific cause will be found to clarify all of these cases.

Nevertheless, nonspecific vaginitis encompasses a broad group which constitutes a large percentage of the total cases of vaginitis. Many of these cases may have resulted from the use of antibiotic drugs, contraceptive jellies, medicated douches, and some drugs used to treat vaginitis. A common factor in these cases may be the destruction of the vaginal Döderlein bacillus and the subsequent disturbance of the vaginal flora and an alteration of the vaginal pH. Significantly, treatment of these patients with only vaginal applications of pure cultures of Döderlein bacillus was found to be practical, rapid, and successful.

Sixty-six years after Döderlein's original discovery, the bacillus named for him still remains an important factor in the preserva-

tion of a normal vagina. These bacteria are also, possibly, a protective mechanism against vaginal invasion by pathogens. Probably the widespread use of many systemic antibiotics and vaginally applied drugs reduces a normal woman's protective mechanism, a pure or predominate growth of Döderlein bacillus, and thus vaginitis may develop more easily.

Thirty-seven years after Schröder's original classification of vaginitis into grades, his method has been found to be of practical value. This method helps, as demonstrated in this study, in the classification of and comparison of therapeutic changes. By substitution of a numerical rating, large groups of cases can be considered statistically and the results plotted on graph paper.

In the cases of vaginitis studied in this report, Döderlein bacillus was rare or absent initially and replacement was, therefore, an obvious and rational consequence. To save time and amount of biological used the initial use of "specific" drugs was justifiable; for example, Mycostatin for monilia vaginitis, Devegan for trichomonas vaginitis, and Terramycin vaginal suppositories for *H. vaginalis* vaginitis. It is an impression gained from this study that concomitant and subsequent use of the Döderlein bacillus with these drugs alleviates symptoms more rapidly, increases the cure rate, and helps to prevent recurrences. In most instances of nonspecific vaginitis, the applications of pure culture of Döderlein bacillus alone were effective. Today, with ever-increasing drug usage, factors which enhance or destroy the normal vaginal flora must be understood.

Summary and conclusions

1. The Döderlein bacillus is usually present in the normal vagina and absent when there is vaginitis.

2. Pure cultures of certain strains of Döderlein bacillus isolated from the vagina of normal women can be cultured and successfully reimplanted in the vagina of patients lacking the bacillus.

3. Lyophilized Döderlein bacillus gave re-

sults comparable to the skim-milk preparation used at first and had the advantages of indefinite preservation, uniformity of bacterial count, and simplicity of use.

4. The study comprised 165 private patients with vaginitis seen in one year, 1958.

5. In Plan A, 134 patients were intensively studied over a period of 6 months. The presence or absence of Döderlein bacillus was determined by a cultural method designed to favor its growth. Patients with vaginitis, lacking the Döderlein bacillus, were treated by applying pure cultures of a special strain of Döderlein bacillus to the vagina. On a subsequent visit a repeat culture was taken to determine the effectiveness of the therapy.

6. Of 44 cases of monilia vaginitis, 25 were treated and studied intensively. With repeated applications, signs and symptoms cleared rapidly and the vaginal flora became predominantly Döderlein bacillus. Mycostatin vaginal suppositories were used in addition only during the first week.

7. There were 47 cases of nonspecific vaginitis. Before treatment 81 per cent of these patients had no Döderlein bacilli in the vaginal flora. They were treated with

only pure cultures of Döderlein bacillus. Of the 19 cases intensively studied, 95 per cent were cured and the vaginal flora of these patients became predominantly Döderlein bacillus.

8. None of the 17 patients with trichomonas vaginitis had Döderlein bacillus in the vaginal flora. These patients were initially treated with pentavalent arsenical as well as with Döderlein bacillus cultures. As the arsenical was stopped and the trichomonads disappeared, further applications of Döderlein bacillus resulted in a nearly predominate growth of this microorganism.

9. The 65 patients in Plan B, some of which were continued from Plan A, gave evidence that similar results could be expected from the use of the lyophilized preparation.

10. Since there is widespread use of systemic and local drugs which destroy the normal vaginal Döderlein bacillus, the proper biological balance should be maintained or restored. This may be accomplished by vaginal applications of pure cultures of a special strain of Döderlein bacillus as reported in this study.

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Furacin (nitrofurazone) vaginal suppositories in operative gynecology

A clinical and bacteriologic study of 137 patients

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THIS study was undertaken to determine the value of Furacin† (nitrofurazone) vaginal suppositories following gynecologic operations and the subjective and objective local effects. Of several methods used by other investigators¹⁻⁷ (Table I), Furacin seemed to offer promise. Certainly, it is preferable to use a single agent rather than multiple ones if this single agent can achieve comparable results. Absence of sensitivity and idiosyncrasy are worthwhile goals.

This synthetic nitrofurazone, whose antibacterial properties were first reported in 1944,⁹ apparently interferes with bacterial respiratory enzymes, blocking an essential step of bacterial metabolism.¹⁰ Furacin does not affect phagocytosis or healing of mammalian tissues,¹¹ its bacteriostatic or bactericidal action on virtually all gram-positive and gram-negative pathogens is not impaired by the

presence of pus, blood, or serum.¹² The drug is widely used as a topical antibacterial in many fields of clinical medicine.¹³ Bacterial resistance and cross resistance with other types of antimicrobial drugs, such as the antibiotics or sulfonamides, has not been reported. Treatment with these suppositories has been reported to give uniformly good results in nonspecific vaginitis,^{14, 15} as has the preoperative use to decrease morbidity following gynecologic operations^{1, 16} and their use postoperatively to lower both the incidence of postoperative infections and the amount of malodorous vaginal discharge.² The suppositories have also been used successfully as an adjunct to radiation therapy of pelvic neoplasms.¹⁷

Our specific objective, therefore, was to evaluate the effect of these suppositories on postoperative morbidity, healing, vaginal bacterial flora, and pH through a study of parallel control and treated cases.

Method and material

This study includes 137 unselected patients treated by various gynecologic surgical procedures ranging from hysterectomies to simple colporrhaphy and colpoperineorrhaphy (Table II) performed at St. Joseph Hospital during an 18 month period ending July 1, 1957. All hysterectomies performed were total in nature. Antibiotics were administered on specific indication only. Each

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†A product of Eaton Laboratories, Norwich, New York.

Table I. Reported results of postoperative vaginal antibacterial therapy

Author	Agent	No. of cases	Operative route	Controls	Preoperative preparation	Postoperative therapy	Morbidity (%)
Cron ⁵	Penicillin	147	Vaginal	None	Zephiran and penicillin	Intramuscular penicillin	23
	Penicillin	260	Both	None	Zephiran and penicillin	Intramuscular penicillin	21
Hofmeister ⁶	Penicillin	147	Vaginal	Not stated	Penicillin	None	16.3
Moore ¹	Furacin	25	Both	None	Furacin	None	0
Pratt ⁷	Penicillin	129	Vaginal	None	Penicillin	None	17.8
	Penicillin and sulfonamides	126	Vaginal	None	Penicillin and intraperitoneal sulfonamides	None	12.7
Schnall ⁴	Penicillin and streptomycin	112	Abdominal	None	Penicillin and streptomycin	Same	8
Schwartz ²	Furacin	48	Both	None	Furacin	Furacin	Not stated
Turner ³	Penicillin	100	Not stated	None	Iodine and penicillin	None	7

patient was placed in one of four categories as described below. Two types of Furacin vaginal suppositories were used—the original 3 Gm. size (0.2 per cent Furacin) and a 2 Gm. size (0.3 per cent)—both in a water-miscible base. The smaller suppository containing the higher concentration was used during the last 3 months of the study. Patients were admitted on the day preceding operation. Total postoperative stay averaged 10 days. Patients who developed morbidity averaged 11 postoperative days.

A. Control group. Preoperative studies included a smear and bacteriologic culture of the posterior forniceal secretions. The material obtained was inoculated into Brewer's thioglycollate broth and tryptase phosphate broth. From the latter broth, both a blood agar plate and an endoagar plate were inoculated. The pH was determined by Nitrazine paper. Operative preparation consisted of thorough cleansing of the perineum and vagina with soap and water, without any specific antiseptics. On the sixth postoperative day a smear and culture were again obtained, pH determined, and vaginal wound healing evaluated and recorded. This group included 49 cases of which 24 were abdominal and 25 vaginal (Table II).

B. Early treated group. A suppository was inserted 14 to 16 hours preoperatively. The usual smear and culture were obtained be-

fore insertion of the suppository and again just preceding operation. No pH readings were obtained in the early portion of this study that comprises this entire group. Operative preparation was identical with the control group. A single suppository was inserted postoperatively each morning, beginning on the first postoperative day and continuing for 5 days. Included here are 35 patients; there were 18 abdominal and 17 vaginal procedures (Table II).

C. Later treated group. In this group, a single Furacin suppository was administered preoperatively. Postoperatively, this agent was used twice daily beginning on Day 1 (C₁). Smears, cultures, and pH readings were obtained as above. Operative preparation was identical to the above description. The total number in this group was 53, including 28 abdominal and 25 vaginal procedures. The higher concentration suppository was used in the latter 23 patients of this later treated group (C₂) (Table II). In a few cases of the parallel later treated and control groups, the bacterial population was gauged by colony counts.

Definitions

Exclusive of the first 24 hours following operation, a temperature elevation to 100.4° F. (38.0° C.) or more on any 2 of the first 10 postoperative days was considered to in-

dicating morbidity (as defined by the American College of Surgeons and the Joint Committee on Maternal Welfare of the United States). Early healing was determined on the basis of the appearance of the vaginal wound as seen on speculum examination of the vagina on the sixth postoperative day. Late healing was similarly determined 4 to 6 weeks postoperatively. If granulation tissue was absent or minimal, healing was considered satisfactory. If granulation tissue was moderate or abundant, healing was felt to be unsatisfactory. Only pH changes of 0.5 unit or more were regarded as significant.

Results

I. Clinical. All observations are detailed in Table III. No deaths occurred in this series.

II. Bacteriologic.

A. Initial flora. *Escherichia coli* was found initially in 67 patients (49 per cent), in pure culture in 38 of these. *Streptococcus faecalis* was noted in 40 specimens (29 per cent). The remaining flora was composed of varied organisms including *Str. viridans*, *Str. hemolyticus*, *Str. nonhemolyticus*, *Str. pyogenes*, *Micrococcus albus*, *M. aureus*, *Bacillus proteus*, *B. subtilis*, *Candida albicans*, and Diphtheroids.

B. Posttreatment flora. The suppository

given preoperatively did not alter bacterial flora qualitatively or quantitatively in the second preoperative specimen in 84 of 88 patients (95 per cent).

Some postoperative (third) cultures revealed changes in gross quantitative terms (i.e., a decrease from marked to few) of bacteria present initially. Twelve of all the treated patients (88) did reveal a decrease in flora, all occurring in the 43 patients having *E. coli* on initial culture. Further, 10 of these 12 were in the later treated group (C_1 and C_2).

C. pH. The initial pH ranged between 5.5 and 6.0, the highest being 6.5, the lowest 4.5. Only two posttreatment pH changes were seen in the lower concentration group (C_1); both were basic in nature. Five basic posttreatment pH changes were noted in the higher concentration group (C_2). There were no significant changes in the remaining individuals.

D. Colony counts. These were performed in 7 patients only, and these late in the study. In 3 cases, there were fewer colonies in the postoperative specimen; in 4 cases, there were more.

III. Side reactions. There was no local irritation or other evidence of sensitivity with either "strength" suppository, nor any evidence of generalized allergy or toxicity.

Table II. Operative procedures

	Control (A)	Early treated (B)*	Later treated (C_1)†	Later treated (C_2)‡
Total	49	35	30	23
Abdominal, total	24	18	15	13
Total hysterectomy	23	16	14	13
Cervicectomy	1	2	1	0
Vaginal, total	25	17	15	10
Hysterectomy and repair§	16	11	13	5
Biopsy and repair§	4	0	0	2
Repair alone§	2	2	0	1
Watkins interposition	2	0	1	1
Cervicectomy and repair§	1	2	1	1
Hysterectomy alone	0	1	0	0
Enterocoele and posterior perineorrhaphy	0	1	0	0

*Single suppository preoperatively and 5 days postoperatively.

†Single suppository preoperatively and two daily postoperatively with lower concentration.

‡As above with higher concentration suppository.

§Repair includes anterior colporrhaphy and posterior colpoperineorrhaphy.

Table III. Postoperative clinical results

	Control (A)	Early (B)*	Later treated (C ₁ and C ₂)	Later treated (C ₁)†	Later treated (C ₂)‡
Total patients	49	35	53	30	23
Operative complication	2	2	0	0	0
Morbidity	8 (16%)	7 (20%)	6 (11%)	4 (13%)	2 (9%)
Early healing					
Satisfactory	48 (98%)	34 (97%)	53	30	23
Unsatisfactory	1 (2%)	1 (3%)	0	0	0
Late healing					
Satisfactory	36 (73%)	32 (91%)	47 (89%)	25 (83%)	22 (95%)
Unsatisfactory	13 (27%)	3 (9%)	6 (11%)	5 (17%)	1 (4%)
pH changes, total	42	0	49	26	23
Acidic	6 (14%)		8 (16%)	5 (19%)	3 (13%)
No change	9 (22%)		25 (52%)	14 (54%)	11 (48%)
Basic	27 (64%)		16 (32%)	7 (27%)	9 (39%)

*Single suppository preoperatively and 5 days postoperatively.

†Single suppository preoperatively, two daily postoperatively with lower concentration.

‡As above with higher concentration suppository.

Comment

Any measure intended to facilitate recovery of operatively traumatized tissue must be evaluated by its effect on morbidity and late healing. Immediate operative complications and early healing as defined in this study depend on hemostasis, surgical skill, and the particular surgical procedure employed. Adequate surgical hemostasis is particularly important since excessive blood loss predisposes to morbidity¹⁸ and to unsatisfactory late vaginal healing.

Further, early healing was found to be a completely unsatisfactory observation, because all patients had a relatively consistent appearance of this 6-day-old vaginal wound. Thus, we are left with morbidity and ultimate healing as yardsticks to gauge the effectiveness of our therapy.

Morbidity in this series, as in all others, is influenced by multiple factors, including the all-important basic surgical principles mentioned above. Presuming these to be constant in our series, uncorrected morbidity was reduced in the later treated cases from a control incidence of 16 per cent to 11 per cent (Fig. 1). A higher incidence, namely, 20 per cent, was noted in the early treated group. Correction of these figures to include only those cases of morbidity due to parametritis and unknown causes reveals a

14 per cent incidence in the controls, 11 per cent in the early treated group, and 8 per cent in the later treated group (Fig. 2). Pertinent details of all morbidities will be found in Table IV.

Further analysis of these figures reveals a stepwise progression in diminution of corrected morbidity incidence by the addition of the suppository once daily, then twice daily, and finally in a higher concentration twice daily.

Statistical analysis, however, reveals the difference here to be nonsignificant, for the observed difference in percentage morbidity is approximately the same as the computed standard error.

The majority were operated upon for benign conditions, although several cases of carcinoma are included. No active pelvic inflammatory disease was noted on ultimate pathologic diagnosis, thereby excluding this factor in the production of morbidity. Only one instance of thrombophlebitis sufficient to cause morbidity was noted.

Our results on morbidity compare favorably with those of Turner,³ who used preoperative penicillin suppositories, the morbidity in his series being stated as 7 per cent. The corrected morbidity in our later treated group was similar (7 per cent). In addition to the antibiotic therapy, he also used an

iodine presurgical preparation. No parallel controls were included in his series. Schnall⁴ reported 8 per cent morbidity with use of penicillin and streptomycin suppositories pre- and postoperatively. All his patients were operated upon abdominally. Details of other investigations as regards antibacterial agent and reported results are detailed in Table I.

Certainly a single agent is to be preferred to a combination of agents, providing comparable results are obtained. The incidence of side effects with use of a single agent, such as Furacin, will necessarily be less than with multiple agents. Penicillin, though an excellent drug with many applications in other fields of clinical therapeutics, should

not be used vaginally in our opinion. Rubin and Boger¹⁹ demonstrated excellent absorption through the intact vaginal mucosa, resulting in even higher blood levels at similar time intervals than could be obtained with oral administration of a similar amount. Beckman²⁰ feels absorption is greater when mucosal inflammation is present, such as is the case postoperatively. Thus, either sensitization, if this is the initial penicillin contact, or allergic manifestations such as urticaria, if there has been previous sensitization, will result in from 1 to 6 per cent of the total population. It is because of this that Welch²¹ questions the value of topically applied penicillin. Goodman and Gilman²² cite the action of the Council on Pharmacy

Table IV. Postoperative morbidity

Portion of series	Cause	Late healing*	Flora	
			Initially	6 days postoperatively
Control (A)	Parametritis	S	<i>E. coli</i> , moderate	<i>E. coli</i>
	Parametritis	U	<i>E. coli</i> , heavy	<i>M. albus</i>
	Hematoma	S	<i>Micrococcus albus</i>	<i>E. coli</i>
	Parametritis	S	<i>E. coli</i> , moderate	<i>E. coli</i>
	Parametritis	U	<i>E. coli</i> , moderate	<i>E. coli</i> , moderate
	Parametritis	S	<i>Str. faecalis</i> , moderate	<i>E. coli</i> , moderate; <i>Str. faecalis</i> , few
	Abdominal wound infection	S	Diphtheroids	<i>Pseudomonas aeruginosa</i>
	Parametritis	U	<i>M. albus</i>	<i>E. coli</i>
Early (B)†	Hematoma	S	<i>E. coli</i> , moderate	<i>E. coli</i> , heavy
	Unknown	S	<i>E. coli</i> , moderate	<i>M. albus</i>
	Parametritis	U	<i>E. coli</i> , moderate	No growth
	Pyelonephritis	S	<i>Str. faecalis</i> ; <i>M. aureus</i>	<i>Str. hemolyticus</i>
	Unknown	S	<i>Str. hemolyticus</i>	<i>E. coli</i>
	Parametritis	U	<i>Micrococcus aureus</i> ; <i>E. coli</i>	<i>E. coli</i>
	Thrombophlebitis	S	<i>M. albus</i> ; <i>Neisseria catarrhalis</i>	<i>N. catarrhalis</i>
Later (C) ₁ ‡	Cystitis	U	<i>E. coli</i> , moderate	<i>E. coli</i> , moderate
	Parametritis	S	<i>M. aureus</i>	<i>Str. viridans</i>
	Cystitis	S	<i>E. coli</i> , heavy	<i>Str. faecalis</i> , moderate
	Parametritis and peritonitis	S	<i>E. coli</i> , moderate; <i>Str. faecalis</i> , moderate	<i>E. coli</i> , moderate; <i>Str. faecalis</i> , moderate
(C) ₂ §	Parametritis	S	<i>E. coli</i> , heavy	<i>E. coli</i> , moderate
	Parametritis	S	<i>E. coli</i> , few	<i>E. coli</i> , moderate

*S = satisfactory; U = unsatisfactory.

†Single suppository preoperatively and 5 days postoperatively.

‡Single suppository preoperatively, two daily postoperatively (lower strength).

§As above with higher concentration suppository.

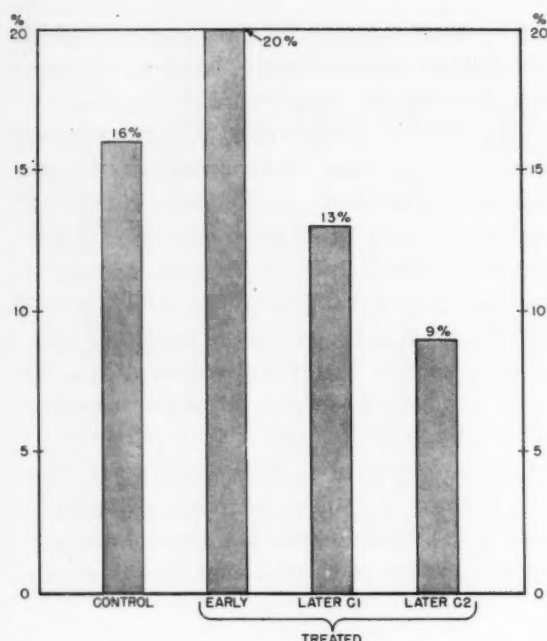


Fig. 1. Morbidity.

and Chemistry of the American Medical Association (1950) in no longer accepting any penicillin preparation designed for topical application for inclusion in *New and Nonofficial Remedies*.

Satisfactory late healing was also enhanced by the use of Furacin vaginal suppositories. Unsatisfactory late healing was noted in 27 per cent of the control group. With a single daily suppository this was reduced to 8 per cent. The use of two suppositories daily of the lower concentration resulted in a 17 per cent incidence. The same twice-a-day regime of the higher concentration preparation reduced this to 4 per cent (Fig. 3). A comparison of all treated cases with the controls reveals a contrast of 27 per cent in the control group and 10 per cent in the treated group. Statistical analysis reveals the computed standard error between control and treated groups, especially the later treated group, to be less than one half the observed percentage difference, thus qualifying this difference as a statistically significant observation.

Diminution of the amount and odor of discharge was noted in those patients with satisfactory late healing. This is certainly

subjective in nature but does seem to be aided to the same degree that satisfactory late healing is by the use of this preparation.

The initial pH averaged 5.5 to 6.0. This is not in accord with the average vaginal pH of 4.7 to 6.3 cited in a recent study by Hunter.²³ The pH initially and postsurgically in the morbid and unsatisfactorily healed cases differed in no way from the average of the entire series.

Postoperative alteration of the pH by the suppositories was not consistent, approximately one half revealing no significant change (Table III). The usual postoperative alkaline change seems to be resisted by treatment as 64 per cent of the controls became alkaline postoperatively while only 33 per cent became such on treatment. This, however, does not seem to be one of the mechanisms whereby Furacin reduces morbidity and promotes ultimate healing.

E. coli and *Str. faecalis* were shown here to be common inhabitants of the vaginal tract, being found in 87 of 137 cases (64

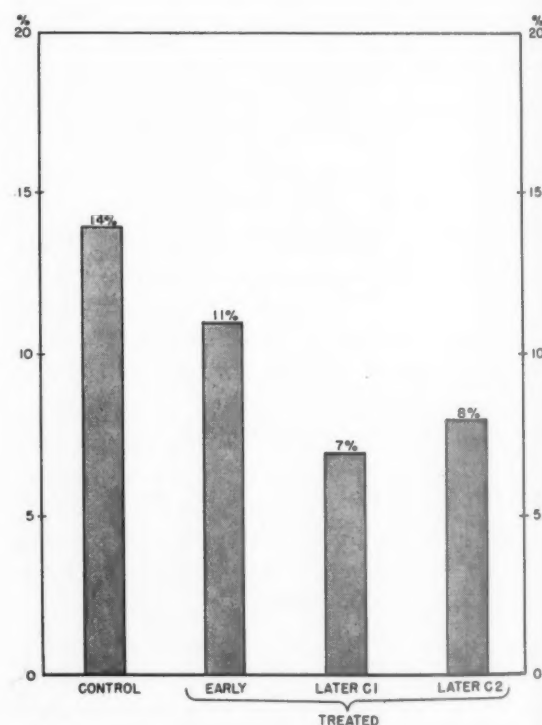


Fig. 2. Corrected morbidity (excludes causes other than parametritis and unknown).

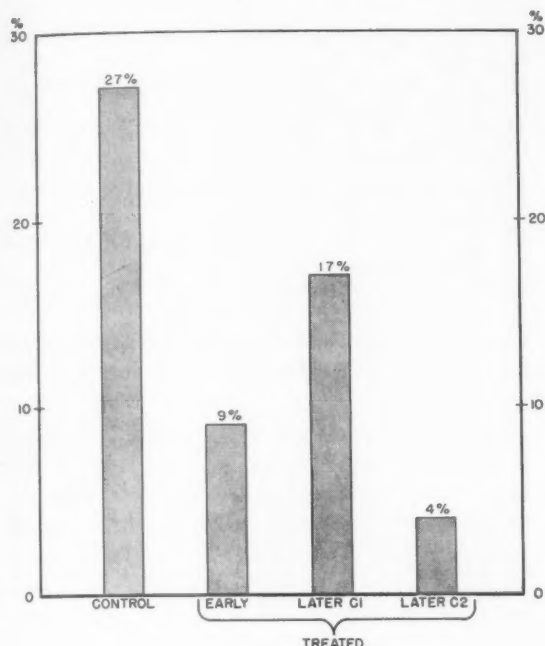


Fig. 3. Unsatisfactory late healing.

per cent). This is at variance with Hunter²⁴ who found one or the other of these organisms in not over 38 per cent of his series of "normal women." The variety of organisms noted here is in accord with his findings. Lactobacilli are not included for, in our opinion, they have no pathologic import per se.

E. coli and *Str. faecalis* are known to be sensitive to Furacin in vitro and in vivo. Clinically, better results were obtained in treated cases as regards morbidity and late healing with the use of this preparation. Probably Furacin acts by bactericidally reducing the number of organisms present rather than by causing their complete disappearance. The normal defense mechanisms of the host may then be able to cope with this diminished number, finally resulting in absence of morbidity and in satisfactory late healing. Quantitative or qualitative floral changes were not remarkable. Only 12 of 43 treated patients (28 per cent) who had either of these organisms initially revealed a quantitative decrease postoperatively. Ten of these were in the later treated group. Comparative colony counts were done in too few cases to evaluate this procedure. It may be

that the answer to why Furacin favorably influences the postoperative course lies here.

There is no correlation between initial flora and the development of morbidity. *E. coli* and *Str. faecalis* were present in approximately the same percentage in the morbid patients as in the entire series (64 per cent). Nor was there any correlation between morbidity due to parametritis and unsatisfactory late healing. One might postulate that parametritis sufficient to produce morbidity would ultimately result in unsatisfactory late healing. Such was not true, for, of 11 patients with morbidity caused by parametritis, only 5 had unsatisfactory late healing. None of the later treated patients with such morbidity had unsatisfactory late healing. The twice-a-day regime would seem to protect the individual from poor healing to some degree.

Summary

1. Corrected morbidity was reduced by the use of Furacin vaginal suppositories. The reduction compares favorably with other reported regimes and has the distinct advantage of being a single agent with minimal to absent side effects.

2. Satisfactory late healing was enhanced to the degree of statistical significance after the use of these suppositories.

3. The apparent lack of correlation between vaginal bacterial flora and clinical performance was noted. This was also true in regard to pH readings.

4. Fewer subjective complaints referable to odor and amount of discharge postoperatively were noted, paralleling the diminished incidence of unsatisfactory late healing in treated cases.

We are deeply indebted to George F. Stevenson, M.D., Director of Laboratories, St. Joseph Hospital, and Dorothy DeBoer, M.T., for their aid in this study.

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Discussion

DR. ARTHUR KLAUANS, Chicago, Illinois. Interestingly enough, all reports on the use of chemotherapeutic agents, antibiotics, or bacteriostatics in the form of vaginal suppositories preoperatively or pre- and postoperatively agree that such a procedure results in a marked diminution in the postoperative morbidity of gynecological patients. I had supposed that by this time we were all using, routinely, a vaginal suppository for such a purpose. Having been associated with the first paper written on this subject, I was convinced of the value of this prophylactic measure 10 years ago.

When Turner presented his paper before this Society on Jan. 20, 1950, his results amazed the audience. He reported a drop in postoperative morbidity following vaginal hysterectomy from 37.5 to 8 per cent merely as the result of the insertion of a penicillin suppository in the vagina on the evening preceding the day of operation. The literature up to that time showed morbidity rates ranging from 26 to 42 per cent. We at Presbyterian Hospital were aware of what Turner was doing at Mount Sinai Hospital because he was using patients of Dr. A. E. Kanter in his study. In order to be prepared for his statistical bomb we began to use his method on our own before his report was presented. In the discussion of his paper, Dr. Edward Allen reported on the small number of his then grand total of 640

vaginal hysterectomies in which the vaginal suppository was used preoperatively. He had a previous morbidity rate of 26.4 per cent. The treated patients developed morbidity in only 8 per cent of cases. At the meeting of the Central Association of Obstetricians and Gynecologists in Houston on Nov. 5, 1953, Dr. Kanter, in the discussion of the paper of Pratt and Scherman, reported on 2,280 vaginal hysterectomies with a morbidity of 13.2 per cent in the patients treated with the preoperative suppository. This group of cases was handled by various members of the attending and resident staffs at the Presbyterian Hospital. Other papers reporting on this method of treatment and its many variations have shown postoperative morbidities ranging between 7 and 23 per cent.

Turner's technique consisted of the use of a single preoperative suppository of 100,000 or 200,000 units of penicillin inserted into the vagina the evening preceding operation. We are still following this pattern with no suppository used following operation. Drs. Grimes and Geiger are getting excellent results with Furacin. Others report good results using suppositories of Bacitracin. Apparently, any effective bacterial deterrent seems to produce the desired result. My feeling is that the bacteriostatic agent diminishes the number of possible pathogenic organisms in the vagina so that at the time of

operation there is a greatly decreased opportunity for the transplantation of these organisms into the peritoneal cavity, the perivaginal spaces, and the vaginal incision. The method works with just the one preoperative suppository because, as I see it, when the operation is completed and the vaginal vault is closed, the further use of suppositories, unless the active ingredients are absorbed and act systemically, would be like placing medicinal agents on the skin wound following an abdominal operation and expecting these to act to prevent infection in the peritoneal cavity.

The postoperative use of suppositories may reduce the amount of odorous discharge. I find no problem with what the authors call "late healing" (all my vaginal vaults are satisfactorily healed when I see the patients for their first postoperative examination 4 to 5 weeks after operation) so I see no need for the postoperative use of suppositories. The choice of agent in the suppository is a matter of personal like or dislike. We have seen no reactions from penicillin during the 10 years we have been using it. Still, when a patient states that she is allergic to penicillin we substitute the Furacin suppository. In using the Furacin suppository over a period of time for the treatment of *Trichomonas* infestations we have seen a number of patients in whom it has produced a local reaction.

I would like to ask the authors how they arrive at the diagnosis of parametritis postoperatively. I do not like to think that they have as many true parametrial infections postoperatively as they report. We rarely see this complication. Most of our infections are in the area between the vaginal vault and the peritoneum where there has been an accumulation of blood and serum. This is readily cured by inserting a finger tip through the vaginal incision and creating drainage. This can be prevented, in most instances, by not suturing the vault too tightly. Four sutures should suffice for this closure—one at each corner and two equally spaced between those.

The authors report on three groups of patients: the early (B) group in which they used one 3 Gm. suppository containing 0.2 per cent Furacin pre- and postoperatively; the later treated (C_1) group in which two of those same suppositories were used each day, and the later treated group (C_2) in which 2 Gm. suppositories with 0.3 per cent Furacin were used twice daily. In Table III, they show a 91 per

cent satisfactory late healing in the B group, an 83 per cent satisfactory result in the C_1 group, and a 95 per cent figure for the C_2 group. From this I am led to conclude that the treatment in the B group is far more efficacious than that in C_1 and almost as good as in C_2 . But the number of patients in each group is so small that the percentage of difference between the several groups is insignificant. So, from their figures we can postulate: $B = C_1 + C_2 = 91$ per cent. We can also state that using our figures for morbidity with the one preoperative suppository only as against their figure for all their groups: Our 8 per cent $= B + C_1 + C_2$ (9 per cent).

I now must conclude with the admission that I have been quibbling. The authors have good results with a method that can help to diminish the postoperative morbidity in gynecological operation. Any report that is added to the literature of the use of any agent in a vaginal suppository that will help to achieve this objective is greatly worth while.

DR. SIDNEY R. LASH, Chicago, Illinois. From 1948 to 1950 Dr. A. F. Lash and I made a study of 200 consecutive vaginal and abdominal hysterectomies using alternate case as controls and culturing the vagina preoperatively and postoperatively on the fourth and eighth days. We used triple sulfa cream pre- and postoperatively daily. We reduced our postoperative febrile morbidity from 40 to 15 per cent. The results were so inferior to those reported by Dr. Turner that we did not report our series at that time. Since that time we have used penicillin vaginal suppositories the night before operation. For over a year our postoperative morbidity was reduced to below 10 per cent. During the past year and a half our morbidity rose considerably despite the penicillin suppositories and we have had to use oral tetracycline postoperatively with a resulting low postoperative morbidity.

After a variable period of time the antibiotics lose their ability to control infection as a result of organism resistance. I think the result of this paper indicates that Furacin is an effective agent for preventing and controlling postoperative infection. However, we must be aware that bacterial resistance may appear at some future time after this drug is used in our hospitals on all of our operated gynecological patients.

DR. WILLIAM H. RUBOVITS, Chicago, Illinois. For many years I have been distressed, in major vaginal operations, by the occurrence of late, severe postoperative bleeding which

sometimes occurred after the patient had been discharged from the hospital. In spite of evidence of mild degrees of local infection in the first postoperative week, good healing usually occurs eventually.

About 15 years ago I began the daily use of Merthiolate vaginal suppositories postoperatively in the hope of improving the morbidity picture and preventing late hemorrhages. I am sure that the purulent, fetid vaginal discharges diminished, and late hemorrhages became a rarity. Unfortunately, I have no statistics for comparison, and my informal experiment received little favorable comment from my colleagues.

I introduced each daily suppository myself and was surprised at the frequency of separation of sutured flaps in the vaginal vault. Primary union of all structures was rare. I believe this is the cause of late hemorrhages.

When Furacin suppositories became available I substituted this remedy for the Merthiolate and also used it preoperatively. I am sure that all the minor complications of the convalescence have been diminished and cases of late hemorrhage have become very infrequent.

DR. GRIMES (Closing). Dr. Klawans is concerned with the term "parametritis." The concept we meant to convey was one of inflammation of the tissues about the apex of the vaginal vault recently traumatized surgically. One might choose paracervical, paravaginal, etc. Since there is of necessity some parametrial tissue present, we chose this term. The difference, therefore, is a semantic one only.

We have mentioned the use of penicillin in other series and the real possibility of sensitivity to this agent. To date, only minimal numbers of such cases have been noted with Furacin, though this may in time be altered. Because of the present paucity of intolerance, idiosyncrasy and/or sensitivity to Furacin as compared with other agents, we feel its use is preferable.

Postoperative use is necessary. In our experience the vaginal wound suture line is incompletely sealed immediately postoperatively. Some operators purposely leave the vault wound open. Penetration of the vaginal antibacterial agent chosen is thus possible into the "parametrial tissues" and healing aided.

Paget's disease of the vulva

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PAGET'S disease of the nipple is considered to be an intraepithelial carcinoma secondary to underlying duct carcinoma of the breast. There is a considerable divergence of opinion, however, as to whether Paget's disease of the vulva represents a primary intraepidermal lesion or is secondary to an underlying apocrine gland carcinoma.^{1-9, 11-14}

Most of the cases of vulvar Paget's disease reported as not being associated with an underlying carcinoma were not studied adequately enough to say with certainty that a small underlying sweat gland carcinoma was not missed. In the case reported here, epidermal changes were found characteristic of Paget's disease; however, no associated apocrine gland carcinoma was found after detailed study of the entire vulva.

Case report

A 58-year-old white woman, gravida i, para i, was admitted to the hospital with a chief complaint of pruritus, irritation, and soreness of the vulva. These symptoms had been present for several months and had been becoming progressively worse.

Past history and review of systems was negative except for a 22 year history of hypertension.

Physical examination. Blood pressure was 255/145, temperature 98.6° F., pulse 92. The general physical examination was essentially normal.

Pelvic examination. There was an area of

clinical leukoplakia of the vulva involving both the labia majora and the labia minora. The skin was tough and leathery. Several small areas of superficial ulceration were evident. No inguinal lymph nodes were palpable. The anal sphincter had an old incomplete laceration. The urethral meatus was red and edematous. The vaginal walls and cervix appeared normal. The uterus was anterior, small, smooth, and mobile. No adnexal masses were felt. The cul-de-sac was normal.

A vaginal smear was reported as Papanicolaou Class III. Biopsies of the vulva were reported as compatible with extramammary Paget's disease.

On June 12, 1957, a simple vulvectomy, uterine curettage, and biopsies of the cervix were performed.

Pathology

Received in the laboratory were two portions of tissue labeled "right vulva" and "left vulva." The skin surface was thickened over the entire specimen except for an outer circumference of 6 to 8 mm. The skin was rough, and tan-white to pearl-white plaques were scattered over the surface. These changes involved the labia majora, the labia minora, and the mucous membrane on the inner side of the labia minora. The skin over the clitoris was thickened and white. No masses were noted in the subcutaneous tissue.

The entire vulva was fixed in 10 per cent Formalin and serially divided into 50 blocks, each 3 to 4 mm. in thickness. Four to six step sections were obtained from each block. Sections were thus obtained at intervals of

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less than 1 ml. through the entire specimen of vulva. All sections were stained with hematoxylin and eosin, and selected sections were prepared with periodic acid-Schiff, mucicarmine, and melanin stains.

Microscopic examination revealed a marked hyperkeratosis and parakeratosis with atypical epithelial hyperplasia in the epidermis. Large, irregular cells were seen individually and in small clumps, particularly in the basal layer of epidermis. These cells were also infiltrating the full thickness of the epithelium and the outer keratinized layer. These cells contained clear, vacuolated cytoplasm and nuclei that were vesicular and which varied in size, shape, and staining quality (Fig. 1). In one area, a group of these cells was infiltrating the underlying superficial stroma. Skin appendages were seen within the underlying corium, and

the same type of vacuolated cells described above were seen surrounding many of the hair follicles (Fig. 2). A marked acute and chronic inflammatory reaction was also noted in the corium. No evidence of a skin appendage carcinoma was seen in any of the sections.

The cytoplasm of the "Paget's cells" readily took up the PAS (Fig. 3) and mucicarmine stains, suggesting that the material within them was mucin. Melanin stains were negative.

Sections of the cervical biopsies demonstrated mild chronic inflammation.

The pathologic diagnosis was: vulva, Paget's disease, with probable early invasion; cervix chronic inflammation.

Repeated examinations since operation have revealed no evidence of recurrence of disease.

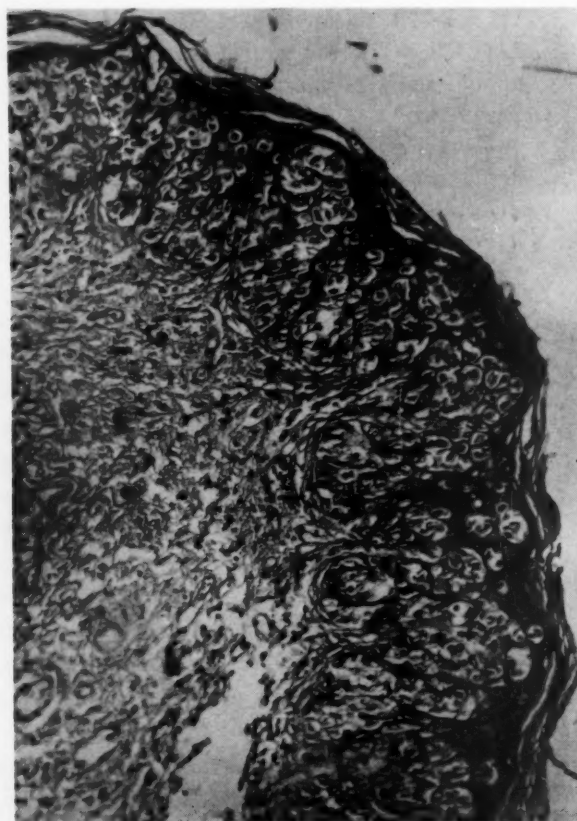


Fig. 1. Numerous Paget cells are seen through the full thickness of the epidermis. (Hematoxylin and eosin. $\times 100$; reduced $\frac{1}{2}$.)

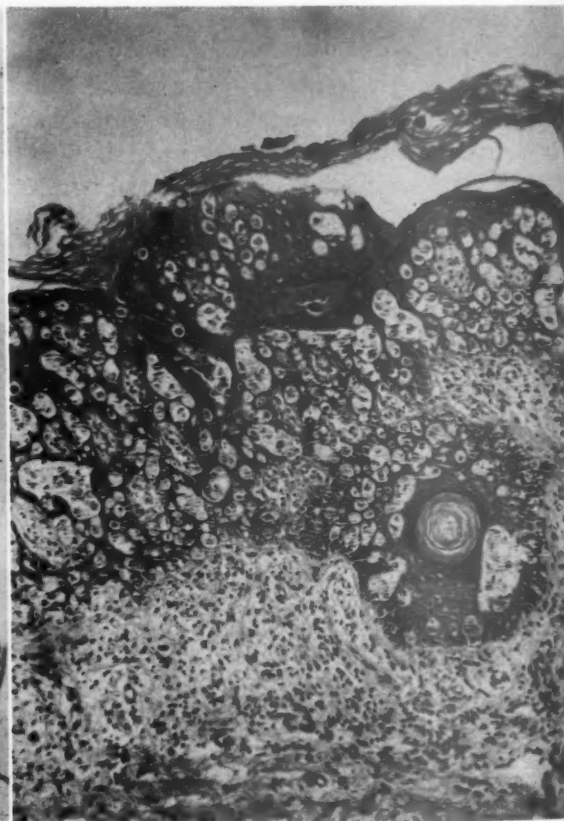


Fig. 2. Paget cells are seen surrounding a hair follicle. (Hematoxylin and eosin. $\times 100$; reduced $\frac{1}{2}$.)

Comment

This case is considered to be one of extramammary Paget's disease. The same microscopic changes were found in the epidermis of the vulva as is seen associated with Paget's disease of the nipple.

Special stains used in studying the microscopic sections demonstrated mucin within the cells. According to Lennox and Pearse,⁹ the presence of mucin in any quantity in a skin tumor is an almost invariable sign of its sweat gland origin. Mucin-containing cells are not seen in Bowen's disease or amelanotic melanoma, whereas they are present in the cells of Paget's disease. Bowen's disease and amelanotic melanoma may be confused with extramammary Paget's disease; however, the presence or absence of mucin-containing cells should help in clarifying the diagnosis.

There is a considerable divergence of opinion as to whether extramammary Paget's disease is ever seen as a primary intraepithelial lesion, or whether it is always secondary to an underlying apocrine gland carcinoma. In most of the reported cases in which no associated underlying apocrine gland carcinoma was found, the vulva had not been adequately studied, and a small underlying carcinoma could easily have been missed. Dockerty and Pratt⁸ reported one case in which serial sectioning of several blocks finally demonstrated a microscopic sweat gland carcinoma. Eisenberg and Theuerkauf⁴ also described an unpublished case in which an underlying ductal carcinoma was confined to a single low-power microscopic field.

Federici⁶ obtained many sections from 10 blocks in the case he reported. No underlying carcinoma was found; however, he does not state if the entire vulva was included in the 10 blocks, or at what thickness the sections were taken.

In the present case, the entire vulva was studied in detail. Sections were taken at levels less than 1 mm. apart throughout the entire vulva. The likelihood of having missed an underlying apocrine gland carcinoma seems very remote and consequently

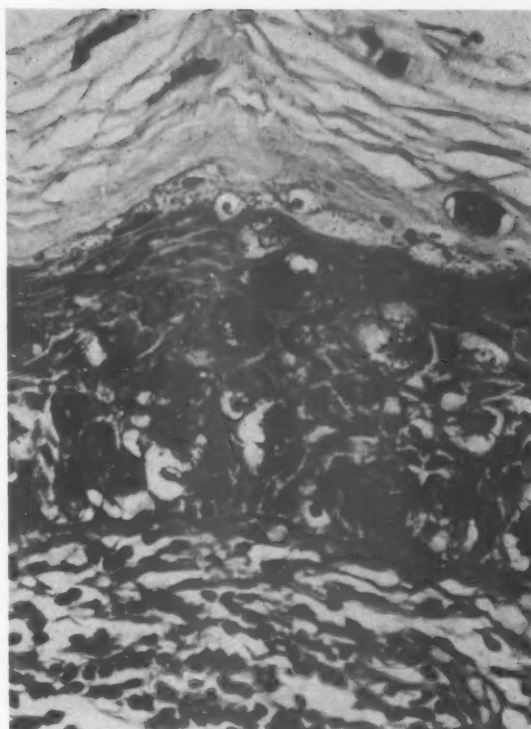
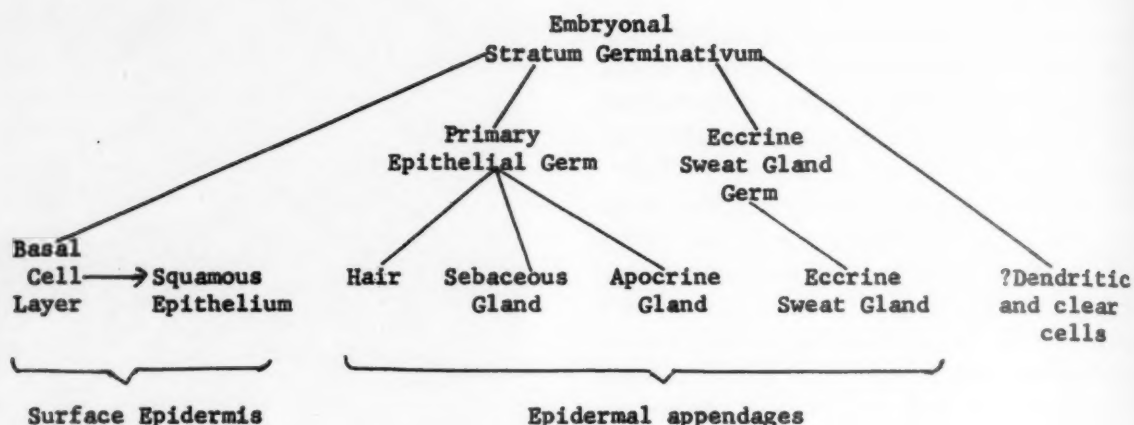


Fig. 3. The PAS stain is readily taken up by the Paget cells as represented by the dark staining areas within the cytoplasm of these cells. ($\times 400$; reduced $\frac{2}{3}$.)

we feel that this case is one of primary intraepithelial extramammary Paget's disease.

Woodruff¹⁴ has stated that, from the accumulated data, Paget's disease of the vulva represents an intraepithelial growth which may progress to invasive carcinoma. The symptoms indicate that the disease is chronic, suggesting that the condition may remain confined within the bounds of the epithelial structures for long periods before invasive tendencies ensue. The lack of an underlying carcinoma and the area of probable early invasion seen in one of our microscopic sections tends to support the theory that this may occur as a primary malignant intraepithelial lesion, which in time will invade the underlying stroma and metastasize.

Several theories have been offered as to the histogenesis of extramammary Paget's disease. The probability of its being an intraepithelial metastasis from an underlying glandular or ductal carcinoma has been

Fig. 4. Embryology of the epidermis.¹⁰

advocated by a number of authors.^{3, 8, 13} Federici⁶ is of the opinion that Paget's disease arises from embryonal rests of undifferentiated nipple tissue along the milk line. Woodruff,¹⁴ in presenting several theories of histogenesis, mentioned that it may arise from the cells of the epidermis involved in the formation of apocrine glands. The latter theory seems quite plausible to us when one considers the embryology of the epidermis (Fig. 4).

The apocrine glands are derived from the primary epithelial germ cells which appear in the third month of fetal life as epithelial buds projecting into the dermis. The primary epithelial germ develops from the inner layer of epidermis (embryonal stratum

germinativum) in the early fetus which also gives rise eventually to the surface epidermis. It is possible that cell rests from the primary epithelial germ or embryonal stratum germinativum with apocrine gland potential may be left in the surface epidermis and that these rests may be the source of intraepidermal Paget's disease.

Summary

1. A case of Paget's disease of the vulva in which detailed microscopic examination of the entire vulva was performed is presented.
2. Our findings suggest that this represents a case of extramammary Paget's disease of epidermal origin.

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Primary carcinoma of the vagina

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THIS report consists of an analysis of the cases of primary vaginal carcinoma at the Royal Victoria Montreal Maternity Hospital during the years 1926 to 1958, inclusive. Twenty-five cases of pathologically proved carcinoma of the vagina were reviewed. The significance of our evaluation of these cases was enhanced by two factors: first, no patient was lost to follow-up, and, second, all patients were actively treated.

General information

Incidence. During the period under study, 2,235 patients with primary malignancy of the female genital tract were admitted to our hospital. The incidence of these malignant tumors by sites is shown in Table I.

Thus, primary vaginal carcinoma accounted for 1.2 per cent of the total. This lies close to the lower limit of incidence found in the literature (Livingstone,⁷ 2 per cent; Ries,¹⁵ 3.2 per cent; Huber,⁴ 3.6 per cent; Bivens,² 1.5 per cent; Moebius,¹⁰ 3.2 per cent; Palmer and Biback,¹³ 1.3 per cent; and Messelt,⁹ 2.6 per cent).

Age. The youngest patient in our series was 35 years old while the oldest was 67. The average age was 50.2. This is in agreement with the observations of most writers.^{7, 9, 10, 13}

Marital status and pregnancies. Twenty-two of the patients were married, 6 were nulliparous, 10 had had from one to four

pregnancies, and 8 had had more than four. All pregnancies had occurred at least a few years prior to the onset of the symptoms.

Menopause. Nineteen patients were menopausal, whereas the remaining 6 were still menstruating at the time when the tumor was diagnosed.

General systemic diseases. These were found in only 3 cases. One patient had diabetes while 2 others had a record of positive serological reactions.

Double primaries. One patient developed cancer of the lungs 4 years after the vaginal tumor was treated.

Causative factors. Of the factors mentioned in the literature as etiologically significant, our series include the following:

1. *Gartner's duct cyst.* One patient had had such a cyst removed from the side which later gave rise to cancer. It is not unlikely that the cancer arose from other Gartner's duct remnants left behind at the time of removal.

2. *"Chronic procidentia."* One patient had suffered from this condition for several years. Operation had never been attempted

Table I. Incidence of malignant tumors, 1926-1958

Site	No.	%
Vulva	64	2.9
Vagina	25	1.2
Cervix	1,313	58.8
Endometrium	415	18.2
Myometrium	54	2.5
Tubes	3	0.2
Ovaries	361	16.2

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to repair this nor had a pessary ever been worn.

3. *Vulvar varicosities.* One patient suffered from extensive varicosities of the vulva and lower vagina but the neoplasm arose in the upper third of the vagina.

4. *Chronic irritation.* One patient wore a large rubber ring pessary for many years. The lesion was situated at the lower end of the posterior vaginal wall. It is likely that this site was subjected to chronic pressure by the pessary.

5. *Menstruation.* Six patients were still menstruating at the time of discovery of the vaginal lesion. This might be of significance to those who speculate about varied concentrations of estrogenic hormones and their carcinogenic potentiality.

In the case of the 18 parous patients, no data could be obtained regarding obstetrical trauma to the lower genital tract.

This scant information does not contribute to our knowledge of the etiology of this disease. We are left with the impression that no one factor is of any value in aiding us in finding obvious inciting causes of this lesion.

Symptomatology. As shown in Table II, a combination of different symptoms occurred in the majority of cases. No patient was entirely symptomless. In general, the symptoms in our series were similar to those observed by other authors, in that (a) the symptoms as such were few, (b) they were frequently obscured for long periods of time, owing to either ignorance or indolence on the part of the patient, and (c) in the majority of cases mild bleeding or blood-tinged spotting was the only symptom manifested.

Table II. Symptomatology

Symptoms	No.	%
Obvious lesion, noticed by the patient	15	60
Spontaneous bleeding	17	
Bleeding on irritation	1	68
Local pain	6	
Pain on irritation	2	32
Weight loss	2	8

The majority of the patients (15) had symptoms of less than 6 months' duration, while 2 patients had symptoms for more than 2 years.

Characteristics of the tumor

The distribution of sites of origin is listed in Table III.

Table III. Site of tumor

Level of lesion	No.	Walls affected	No.
Lower third	3	Anterior	1
Middle third	3	Posterior	8
Upper third	9	Unilateral	10
Lower third	5	Anterior	1
Middle third		Posterior	
Middle third	4	Posterior	2
Upper third		Unilateral	
Lower third	1	Anterior	1
Middle third		Unilateral	
Upper third		Circular ("cork-screw")	2
Total	25	Total	25

It is obvious that, as expected and repeatedly reported in the past, the upper third of the vagina (57.7 per cent in our series) and the posterior wall (53.8 per cent in our series) were involved as the primary site in more than half the cases. These are the sites in the vagina which are continuously exposed to a variety of physical and chemical irritants, both intrinsic and extrinsic. In 9 cases, the tumor was unicentric while in 4 it was multicentric. In the remaining 12 cases either this was not described or the lesion was widespread.

Form of the tumor. Eleven of the tumors were ulcerative, 6 were fungating, and 2 were both ulcerative and fungating, while 6 cases lacked sufficient description to be classified.

Size of the tumor. The review afforded only an approximation of the actual size of the lesion. Six measured from 1 to 3 cm. in diameter, 16 measured over 3 cm. in diameter, and in 3 cases the size of the lesion was not specified.

Staging of the tumor. No staging of any kind was used throughout the years within which this series was accumulated. A post hoc staging would necessarily be unsatisfactory on the whole. The data available on the size and form of the tumor were not accurate enough to allow a retrospective staging in all cases.

Pathology. All the tumors were of the epidermoid variety except one which, after repeated reviewing, was classified as a transitional cell carcinoma. Since this tumor was located in the upper third of the vagina and limited to the lateral wall, we may speculate on a Gartner's duct origin. No adenocarcinoma was found in the series. A grading of the lesion was carried out. Sixteen cases were labeled as anaplastic and 6 as differentiated, while 3 could not be graded with certainty.

Treatment

During this 32 year period, treatment was modified repeatedly so that significant assessment of these modifications seems possible today. As illustrated in Table IV, there were 7 different methods of treatment used.

The differences consisted in variations in the dose of radium and x-ray and in the use of different radium applicators. The sixth group consists of one patient treated with a central linear source of radium and partial operation, while the seventh group consists of one patient treated by radical operation. In both patients this was planned and performed as the primary treatment.

Substandard radium doses varied between 2,100 and 4,500 mg. hr. and in one in-

stance only 600 mg. hr. was given. The standard cervix radium dose used was 6,000 mg. hr. in divided doses. With the central linear source of radium, the dose was calculated in roentgens to the surface of the vaginal wall. A surface dose of 4,800 to more than 9,000 r was given to those patients selected for this type of treatment. In 11 cases (44 per cent) in which it was thought that the chosen optimal dose would not suffice, this was combined with deep x-ray therapy. As with the radium dose, the additional amount of x-ray differed in each case depending on the tolerance of the patient and the extent of growth into surrounding tissues. Additional deep x-ray therapy was given in doses as small as 2,132 r in one case, but in most this varied from 3,000 to 9,000 r. In one case 11,000 r was given and in another 17,000. The field distribution and fractionation of the total irradiation were likewise individualized.

Those patients who did not survive one year were in Groups 1, 3, and 6, one in each. Of those who survived 2 years, one patient belonged in Group 1 and 4 to Group 3. Those who survived 3 years fell into Groups 1 and 3, there being one in each. Finally, there was one 4 year survivor in Group 2. Our 11 cases of 5 year survivors, representing 44 per cent, have been analyzed in an attempt to discover what factors have led to this encouraging result. In the following paragraph we present the data concerning this group of patients.

The ages varied between 36 and 65 years, with an average of 52.9. Six of the patients were parous and 3 nulliparous. The lesion in 7 was larger than 3 cm. in one dimen-

Table IV. Mode of treatment

Group	No. of cases	Type of treatment	5 year survival
1	9	Radium, cervix type applicator, substandard dose	7
2	3	Radium, central linear source	2
3	8	Radium, cervix type applicator, substandard dose, and deep x-ray	-
4	2	Radium, cervix type applicator, standard dose, and deep x-ray	1
5	1	Radium, central linear source, and deep x-ray	1
6	1	Radium, central linear source, and partial operation	-
7	1	Radical operation	-
Total	25		11 (44%)

sion; in 2 patients it exceeded 2 cm.; and in 2 this was not described. Four of the 5 large tumors were described as ulcerative, while the others were described as either fungating or ulcerative. In 5 cases the tumor was anaplastic, while in the remainder it was classified as differentiated. Among those who have died, one patient died after 17 years because of a coronary thrombosis and was free of tumor; one died after 5 years of cachexia, with tumor; one died after 6 years of unknown cause and with tumor. It is interesting that the majority of our survivors (7 out of 11) were treated with a substandard dose of radium by means of a cervical type of applicator. Of the remainder, 2 patients received 5,000 r of radium, from a central linear source, and another a standard dose of radium with a cervical applicator and an additional 9,500 r as deep x-ray therapy. The last patient in this series received 8,280 r from a central linear source as effective radiation to the vaginal wall and additional deep x-ray therapy with an estimated dose of 1,878 r to the deepest portion of the pelvis and vagina. This patient is one of 2 of the 5 year survivors who developed complications due to therapy. A rectal stricture due to radiation fibrosis became manifest one month after completion of therapy, necessitating a transverse colostomy. Three months later this patient developed a large rectovaginal fistula for which an abdominoperineal resection and subtotal colectomy were performed. Five months after this, a large vesicovaginal fistula appeared and was treated by a uretero-ileo-cystoplasty. The patient progressed satisfactorily for the following 8 months when further operation was required to correct a herniation of the bladder. This patient is still living and remains free of tumor to this date. The other complication was a simple vaginal stenosis which required no treatment.

Recurrence. We labeled as a recurrence any regrowth of the same type of tumor at the site of the primary lesion or in its close proximity discovered at any time after the planned course of treatment was com-

pleted. In these cases it was not easy to ascertain whether we were dealing with a true recurrence or with primary extension, present initially, but not recognized as such. Differentiation between spread into paravaginal spaces, inflammation, and fibrosis was particularly difficult, as were attempts to pinpoint the time of recurrence. In all but one of our 6 cases of recurrence, this occurred on the upper, posterior third of the vaginal wall, and it involved the cervix in one instance. In one case, this was observed in the lower two thirds of the vagina, and, in a last case, infiltrative growth was found with the primary tumor at the anterior wall of the middle third of the vagina. In 3 of the cases of recurrence, inguinal metastases were found as well. The recurrences were all treated by additional deep x-ray therapy except for the bladder recurrence which occurred terminally.

Metastases. Classified as metastases were those lesions of the same pathological nature as the primary lesion, and found at another site, either simultaneously or at a later date, including postmortem findings.

Metastases were found in 8 instances (32 per cent). In 7 of these, inguinal glands and, occasionally, other glands were involved. Two of these 7 patients developed bony metastases while a third showed carcinomatosis shortly after primary radical operation. As part of the initially planned treatment, the majority received additional deep x-ray therapy. In one case, bilateral block dissection was carried out at the time of radium application. The eighth patient developed lung metastases and no treatment was given for this. Only 2 of these 8 patients survived as long as 4 years.

Complications. Save for metastases or recurrences, any sequela arising as either the direct result of the malignancy or of its treatment, during or after therapy, was considered a complication.

These arose in 9 cases (36 per cent). Their nature, the mode of treatment, and survival rates were illustrated in Table V. Treatment was not instituted in cases of

Table V. Complications

Complication	Treatment	Survival
Vaginal stenosis	—	8 years
Rectal stenosis	Colostomy	4½ years
Rectovaginal fistula	—	16 months
Rectovaginal fistula, rectal stenosis	Colostomy	4 years
Vesicovaginal fistula, rectal stenosis	—	15 months
Rectovaginal fistula, vesicovaginal fistula, stenosis of vagina and rectum	Abdominal-perineal resection, colostomy, ureteroileo-cystoplasty, partial cystectomy	5 years (still alive)
Vesicovaginal fistula, sepsis, pelvic abscess, intractable pain	Colpotomy, chordotomy	1 year
Intractable pain	Chordotomy	5 years
Abscess of metastatic inguinal gland after deep x-ray therapy	Incision of abscess	3 years

asymptomatic complications or where the extent of the disease was such as to militate against any treatment, definitive or palliative. In 5 patients there were 3 rectovaginal fistulas and 3 vesicovaginal fistulas, one patient having both. Analysis of these cases failed to reveal any single initial etiological factor. The sites of the primary lesions did not suggest that a relation existed between this and the adjacent organ into which fistula formation occurred. The fact that only one of these patients has survived more than 4 years may indicate that we are dealing here with an inherently refractory lesion. It seems improbable that radiation alone was the cause of these fistulas, since both radiation dosage and the means of administration varied from case to case.

Causes of death. Sixteen out of our 25 patients were dead at the time of writing. The causes of death were as follows: cachexia (with tumor) 10, cachexia and hemorrhage (with tumor) 2, hemorrhage (with tumor) 2, cachexia and uremia (with tumor) 1, and other causes (free of tumor) 1.

Comment

The fact that among more than 2,200 primary malignancies of the female genital tract only 25 cases of vaginal lesions were

found emphasizes once more the rarity of the disease. Moebius,¹⁰ in his excellent review of reports on primary vaginal carcinoma, lists 54 contributions from the world literature published during the years 1895 to 1955. Among these, 40 publications dealt with series of up to 40 cases, more than half of them representing series of less than 25 cases.

The review of the characteristics of patients and tumors revealed no worthwhile conclusions. All of them are within the range of information which has been given before and, once more, underline the fact that there are very few specific characteristics common to all of them. The extreme rarity of adenocarcinoma is borne out in our series.

As for adaptation of a mode of staging for the future, we found a few suggestions in the literature, each more inadequate than the other. It is our impression that the main obstacle is the uncertainty with which spread through and beyond the vaginal wall and into paravaginal tissues can be estimated on examination. Murphy,¹¹ in his paper, introduced a type of staging which seems to us too directly linked with his mode of treatment and, therefore, not generally applicable. If any mode of staging gives promise, it is Courtial's.¹⁷ He suggests the following breakdown:

Stage I. The tumor is strictly limited to the vagina and has not invaded the muscularis. It may be nodular or a shallow ulcer, not extending over more than one half of one wall, e.g., not larger than 3 cm. in its largest diameter.

Stage II. The tumor extends through the muscularis into adjacent tissues and spaces (ischiorectal fossa, etc.). The tumor is not fixed to the pelvic wall.

Stage III. The tumor is fixed to the pelvic wall, possibly involving surrounding organs such as the bladder, urethra, or rectum.

The fact that all suggestions of treatment so far made do not approach a standard is also reflected in our series. As the number of years within which this series has been accumulated expands over more than 3 decades, naturally, different modes of treatment have been applied by different workers. It surprised us to discover that radium applications of the cervix type in substandard dosage without additional deep x-ray therapy gave us the majority of our 5 year survivors. Since our survival rate is quite satisfactory in comparison to other reports, we may claim that this method of treatment is recommended. It is, of course, understood that it will not be applicable in all cases, and central linear sources will

be needed in a number of instances where the middle and lower thirds are involved.

Our experience with primary radical surgical treatment is too small to permit any conclusions. Despite careful patient selection our results were not good. We also note a paucity of good results from this form of treatment in the recent literature.^{6, 8} In view of the above, we shall probably continue to treat the upper one third lesions with cervix-type radiation and hope that our apparent good results will continue.

Summary

1. A series of 25 primary vaginal carcinomas has been presented.
2. History, predisposing factors, symptomatology, and characteristics of the tumor have been presented in detail.
3. The value of staging the tumor has been discussed.
4. A survey of the treatment with particular analysis of the 5 year survivors is given.
5. The place of radical operation is discussed.
6. Our 5 year survival rate of 44 per cent is discussed.

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Basal cell and basal-squamous cell carcinomas of the vulva

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BASAL cell carcinoma of the vulva, though admittedly rare, has received little attention in the gynecologic literature. Authors have often omitted the lesion from classifications of vulvar malignancies or, if recording the lesion, have failed to describe its histogenesis and histopathology, particularly with regard to differentiation to a basal-squamous cell lesion. The purpose of this paper is to report one basal cell and 3 basal-squamous cell carcinomas of the vulva and to emphasize the potential of differentiation of a basal cell tumor to a basal-squamous cell carcinoma, a lesion of added import.

Histogenesis

There are a number of theories concerning the site of origin of basal cell carcinomas: (1) basal cells of the epidermis, (2) hair matrix cells, (3) pilosebaceous apparatus, (4) hamartomas, and (5) multicentric origin.

Krompecher,²⁶ in 1900, considered the lesion to arise from embryonal basal cells and described solid, glandular, cystic, and parakeratotic types. Mallory,³³ in 1910, demonstrated fibrils identical with those in embryonal hair follicles and was among those²¹ supporting the origin from hair matrix cells.

Foot¹⁸ demonstrated nerve plexuses in the pilosebaceous apparatus but not in the basal layer of the epidermis; he stated that adenexal carcinoma, where heavy bundles of

nonmyelinated fibers can be demonstrated in the stroma, is therefore related to hairs, sebaceous glands, and sweat glands and not to the basal layer of the epidermis. Lever³¹ believes that basal cell lesions are nevoid tumors (hamartomas) derived from embryonal primary epithelial germ cells which can differentiate into sebaceous glands ("cystic" type), sweat glands ("adenoid" type), and hair ("keratotic" type).

Willis⁶⁴ and others⁵⁸ support the most acceptable theory of multicentric origin from the epidermis itself, from the pilosebaceous apparatus, or from both.

The complexity of the histogenesis is heightened by disagreement concerning the existence of a basal-squamous cell carcinoma. Certain investigators^{30, 31, 63} consider the so-called basal-squamous cell type to be in reality a keratotic basal cell carcinoma.

It has long been accepted that squamous cell carcinoma arises from the epidermis and that basal cells, by progressive differentiation, develop into squamous cells, granular cells, and horny cells of the epidermis. On the basis of the process of keratinization,² squamous cell carcinoma must also arise from the basal layer since this is the actively growing layer of the epithelium. Montgomery³⁴ believed that it was impossible for squamous cell carcinoma to arise from "squamous cells" since, as Broders^{5, 6} emphasized, cells that show signs of keratinization are not capable of further reproduction, and such cells in tumors are not active cancer cells.

It therefore does not appear unreasonable to assume that the cells of a basal cell

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carcinoma may undergo progressive transformation to squamous cells so that a basal-squamous cell lesion may be encountered. Indeed, many such lesions in various locations of the body have been reported, often with incontrovertible photomicrographs.^{5, 8, 11, 15, 19, 20, 22-25, 32, 34, 36, 43, 45, 46, 64} It is interesting to note the supporting evidence that several reported "metastatic" basal cell carcinomas proved on further study to be mixed or basal-squamous cell tumors with the metastatic lesions composed of malignant squamous cells. Schrek,⁴⁶ in studying 300 basal cell tumors of the skin, reported that only one gave rise to metastatic nodes. This metastasis was in a basal-squamous cell carcinoma, and it was the squamous portion which metastasized.

It appears that the stringent distinctions which are too often made between basal cell carcinoma and squamous cell carcinoma may be misleading. Both lesions are histogenetically related, and the occurrence of basal-squamous cell carcinoma serves to call our attention to this relationship.

Clinical features

Incidence. Approximately 80 cases of basal cell carcinoma of the vulva have been reported. Corscaden¹⁰ cites the incidence of basal cell carcinoma as 2 to 4 per cent of vulvar malignancies, while Ward⁵⁷ states that the lesion accounts for 0.4 per cent of all female genital tract malignancies.

When the case to be presented here is combined with 13 other reports^{1, 13, 14, 39, 41, 44, 48, 50, 52, 60-62, 65} in which basal cell carcinomas are recorded in relation to other vulvar malignancies, it is found that a total of 41 basal cell lesions occurred among 1,499 vulvar malignancies, an incidence of pure basal cell carcinoma of the vulva of 2.7 per cent.

The incidence of basal-squamous cell carcinoma is difficult to evaluate because of the aforementioned lack of agreement concerning its existence. With regard to the skin in general, the incidence of the basal-squamous cell lesion, when 3 large studies^{40, 59, 66} are combined, averages 10.4 per

cent. With regard to the vulvar area, a combination of the cases mentioned in 6 reports^{9, 14, 36, 44, 45, 48} with the 3 cases to be reported here yields 10 basal-squamous cell lesions occurring among 399 vulvar malignancies, an incidence of basal-squamous cell carcinoma of the vulva of 2.5 per cent.

Age. Basal cell carcinoma of the skin has been reported in children⁴⁷ though the majority of reports concern the older age groups. Lennox and Wells³⁰ found the mean age of 150 patients with basal cell carcinoma of the skin to be 65; Thackray⁵⁵ noted the highest incidence in the age group 70 to 74.

With regard to basal cell carcinoma of the vulvar area, the average age in a review of 65 cases⁴⁸ was 63 years. The youngest patient appears to be 36 years old,³⁵ while the oldest appears to be 86.⁴⁸ The ages of the 4 patients to be reported here are 48, 64, 69, and 71.

Site. The labium majus is the most common site. Wilson⁶⁵ reported the site in a group of cases to be labia majora 11, labia minora 2, meatus 3, and clitoris 2, and he stated that there is no essential difference in this respect from squamous cell carcinoma. The vulvar lesion may be multiple^{4, 17, 54} and may be associated with similar lesions elsewhere on the body.¹⁷ Two cases are reported to have occurred at the site of a vulvectomy scar.⁵⁷

Clinical picture. Pruritus, burning, discharge, and chronic ulceration are common; bleeding is unusual except in large or long-standing lesions. The lesion may present clinically as (1) the nodulo-ulcerative type, pigmented or nonpigmented, with a pearly overhanging border; (2) the fibrosing or morphea-like type with a slightly elevated, firm, waxy poorly demarcated lesion where ulceration occurs late; or (3) the superficial or erythematous type without ulceration or with only superficial ulceration and occasionally with a sclerotic scar. At times, inflammatory inguinal lymphadenopathy may accompany a large necrotic lesion.⁶⁵ As with many vulvar lesions, a history of significant delay in seeking treat-

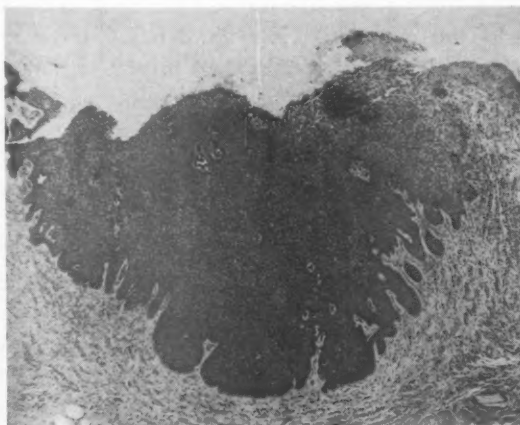
ment or of poor response of a chronic ulcerative lesion to various medications is elicited. In one study,⁴⁸ the interval from onset of symptoms to onset of treatment averaged 6.6 years; others have noted a history of vulvar pruritus for as long as 20 to 30 years.^{4, 7}

Predisposing factors. Syphilis has occasionally been suggested as a precursor though adequate statistical evaluation is lacking. The stated relationship between leukoplakia and squamous cell carcinoma does not appear to exist with basal cell carcinoma.⁴⁸ Chronic pruritus vulvae is often salient in the history, but its etiological significance has not been established; 3 cases have been recorded where a basal cell carcinoma developed in patients who had undergone a partial vulvectomy for pruritus vulvae.^{4, 56, 65} The lesion has been noted following the use of arsenicals⁵⁷ and also after irradiation of the vulva for pruritus⁵⁷; others^{38, 67} have called attention to the tendency for patients treated by irradiation for cervical carcinoma to subsequently develop vulvar carcinoma more commonly than anticipated statistically. Basal cell carcinoma of the vulva seems to be less common in Negroes than in Caucasians.⁴⁸

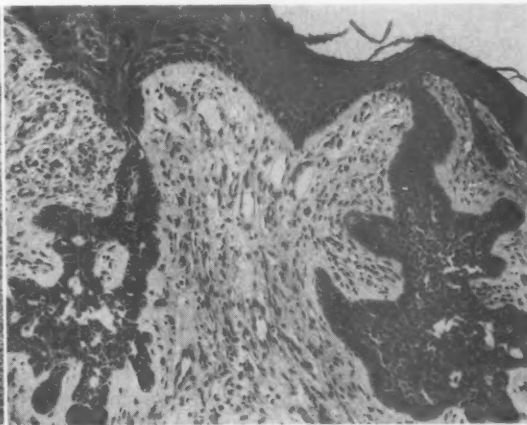
Histologic characteristics

Pure basal cell carcinoma is composed of densely packed cells of fairly uniform size with oval or somewhat fusiform shape, showing dark nuclei separated by a thin rim of cytoplasm. Intercellular bridges are usually absent in contrast to those observed between basal cells of the normal epidermis; mitotic figures are fairly common. The basal cell groups may be in the form of single or multiple growths from the basal layer of the epidermis (Figs. 1 and 2) or from the hair shaft or glandular apparatus. A fairly characteristic layer of cuboidal or columnar cells in a palisading arrangement is quite often noted, similar to the basal layer of the normal epidermis (Figs. 2, 6, 7, and 8). Melanin may be noted in a fair proportion of cases.^{3, 20}

A moderate inflammatory reaction may or may not be present in the adjacent connective tissue, which often undergoes a mucinous degeneration with apparent retraction of the tissue since mucin shrinks during fixation (Fig. 5). Attention has been called to this fact as an aid in distinguishing basal cell carcinoma from other lesions.³¹ Ulceration may occur; occasionally, a pseudoepitheliomatous hyperplasia, which the inexperienced observer may confuse



1



2

Fig. 1. Case 1. Pure basal cell carcinoma with peripheral palisading and superficial ulceration. (Hematoxylin and eosin. $\times 45$; reduced $\frac{1}{3}$.)

Fig. 2. Case 1. Basal cell carcinoma proliferating directly from the basal cells of the epidermis

with peripheral palisading. Note intercellular bridges present between basal cells of the normal epidermis but absent between cells of the carcinoma. (Hematoxylin and eosin. $\times 135$; reduced $\frac{1}{3}$.)

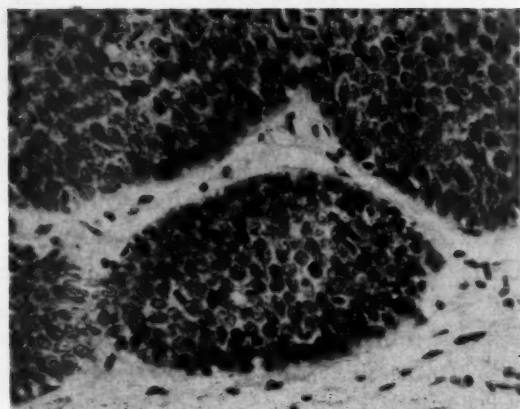


Fig. 3. Case 2. Basal-squamous cell carcinoma showing in this view deeply staining basal cells of fairly uniform size and shape with only an occasional intermediate cell suggestive of differentiation toward a squamous cell. (Hematoxylin and eosin. $\times 425$; reduced $\frac{1}{3}$.)

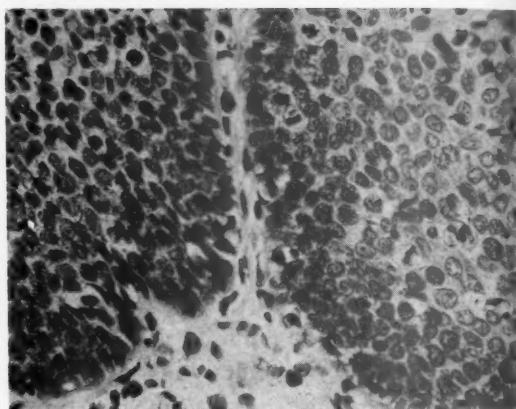


Fig. 4. Case 2. Same lesion as in Fig. 3 showing differentiation (more pronounced on the right) to cells which are variously shaped, somewhat larger, and lighter staining with multiple nucleoli and prominent mitoses. (Hematoxylin and eosin. $\times 475$; reduced $\frac{1}{3}$.)

with squamous cell carcinoma, is noted adjacent to the area of chronic ulceration.

Darier and Ferrand,¹¹ in 1922, referred to three types of basal cell lesions: (1) *épithéliome basocellulaire* or pure basal cell type, as in Fig. 1; (2) *épithéliome métatypique mixte* with a mixture of deeply staining basal cells and lighter staining prickly cells with attempts at pearl formation, as in Fig. 5; and (3) *épithéliome métatypique intermédiaire* where cells intermediate between basal and prickly cells are seen; these variously shaped cells are somewhat larger and lighter staining than basal cells and contain multiple nucleoli and prominent mitoses, as in Fig. 4. While some investigators maintain this classification, others refer to both of Darier's latter two groups as the basal-squamous cell type.

Among 75 cases of carcinoma of the vulva recorded at Stanford University Hospitals during the period 1916-1958, one basal cell carcinoma and three basal-squamous cell carcinomas were noted, an incidence of 1.3 and 4.0 per cent, respectively.

Case reports

Case 1. A 71-year-old white woman, para 3-0-0-3, complained of pruritus vulvae for $1\frac{1}{2}$ years as well as of a "lump" in the right labium majus for 3 months. The past history included a

uterine suspension 26 years previously, a total hysterectomy for leiomyomas 20 years previously, and a cholecystectomy and an anterior colporrhaphy $1\frac{1}{2}$ years previously. When the patient was first seen, the pertinent finding was a pea-sized, firm, nodular lesion with a small central ulceration and a pearly border located on the right labium majus; there was no lymph node enlargement. A wide excisional biopsy confirmed the clinical impression of basal cell carcinoma. Microscopically, there was an area of solid downgrowth of basal cells with peripheral palisading and superficial ulceration (Fig. 1) in addition to other areas with minimal adenoid tendency originating directly from the basal layer of the epidermis (Fig. 2). No intermediate or squamous cells were evident in any section. Immediately after the biopsy in October, 1958, a wide complete vulvectomy was performed. No malignant areas were noted in multiple sections of the specimen. The patient is currently alive and well and is without recurrence.

Diagnosis. The diagnosis was basal cell carcinoma of the vulva (*épithéliome basocellulaire* of Darier).

Case 2. A 48-year-old white woman, para 0-0-0-0, with a history of radium and external irradiation treatment in January, 1952, for Stage II carcinoma of the cervix, complained of vulvar itching of "several years" duration. Her last menstrual period occurred 3 months prior to the irradiation therapy. In November, 1952, a nodular, erythematous lesion, 1.5 by 1.0 by 0.5 cm.,

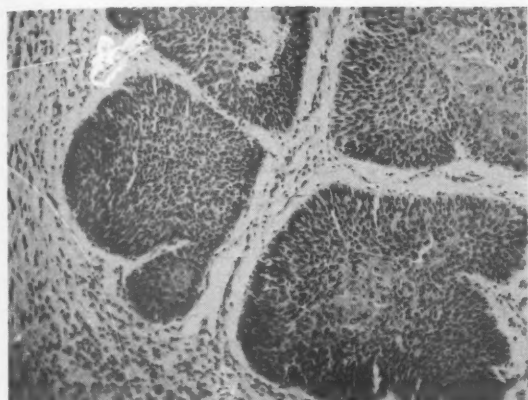


Fig. 5. Case 3. Basal-squamous cell carcinoma composed of deeply staining basal cells with areas of lighter staining intermediate and squamous cells. Note slight retraction of adjacent tissue due to mucinous degeneration. (Hematoxylin and eosin. $\times 135$; reduced $\frac{1}{3}$.)

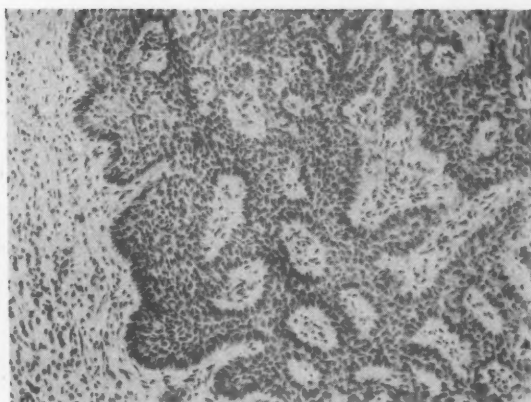


Fig. 6. Case 4. Basal-squamous cell carcinoma showing in this view a lacelike arrangement of pure basal cells with prominent peripheral palisading. (Hematoxylin and eosin. $\times 135$; reduced $\frac{1}{3}$.)

on the lowermost portion of the right labium minus was treated by wide excision of the fourchette and lower half of the labium minus. There were no palpable nodes or evidence of distant metastasis. Microscopic examination revealed a large area of basal cell proliferation with several areas of early cystic degeneration. In sharp contrast to the pure basal cells in most sections (Fig. 3) were other areas in which cells intermediate between basal and squamous cells were prominent (Fig. 4); these intermediate cells were larger, eosin-staining cells of varying shape with frequent mitoses and were considered to be basal cells differentiating toward malignant squamous cells. No penetration beyond the basement membrane could be demonstrated. The patient is currently alive and is without recurrence.

Diagnosis. The diagnosis was basal-squamous cell carcinoma of the vulva (*épithéliome métatypique intermédiaire* of Darier).

Case 3. A 69-year-old white woman, para 3-0-1-2, with a history of total hysterectomy at age 26 for "excessive bleeding," complained of itching of the entire vulva for "many years." A biopsy examination of the left labium majus in February, 1942, was interpreted as indicative of leukoplakia. In May, 1942, a 1.5 by 1.0 cm. slightly raised white patch in the midportion of the left labium majus was treated by wide local excision. Microscopic examination revealed groups of deeply staining basal cells with peripheral palisading; other sections showed

groups with similar basal cells but with prominent areas of prickly cells with eosin-staining central portions (Fig. 5). Multiple sections showed attempts at pearl formation in varying degrees but no squamous component could be seen to invade beyond the basement membrane. The patient was last seen in 1947 without evidence of recurrence but died one year later of cardiac disease in another city. No autopsy was performed.

Diagnosis. The diagnosis was basal-squamous cell carcinoma of the vulva (*épithéliome métatypique mixte* of Darier).

Case 4. A 64-year-old white woman, para 0-0-0-0, whose menopause was 11 years previous, complained of "many years" of vulvar burning. Past history revealed a mastectomy in 1919 for carcinoma. When first seen in 1950, a pea-sized, raised, ulcerated lesion in the midportion of the right labium majus was removed under local anesthesia. No nodes were palpable. Microscopic examination showed in one area a lacelike pattern of basal cells with prominent peripheral palisading (Fig. 6); no squamous component was evident. Other sections, however, showed a distinct change from the peripheral deep-staining basal cells to eosin-staining intermediate and prickly cells with attempt at pearl formation (Fig. 7); in this particular area, no penetration of squamous cells beyond the basement membrane was discernible nor were there striking malignant characteristics to the squamous cells. However, in another section close

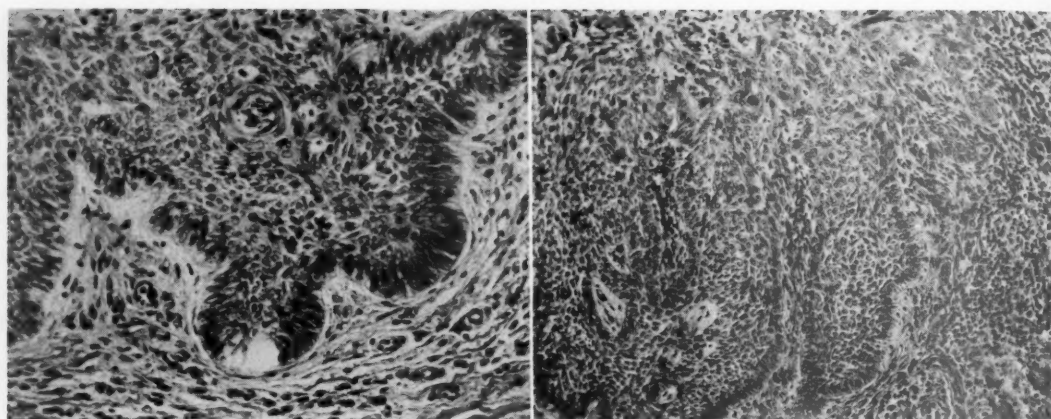


Fig. 7. Case 4. Same lesion as in Fig. 6 showing peripheral basal cells with progression to lighter staining squamous cells. Note keratotic area in center composed of concentric layers of squamous cells. (Hematoxylin and eosin. $\times 225$; reduced $\frac{1}{3}$.)

Fig. 8. Case 4. Same lesion as in Figs. 6 and 7 showing the same palisading arrangement of peripheral basal cells but with the major portion of the lesion composed of malignant squamous cells invading the surrounding stroma with a marked inflammatory reaction. (Hematoxylin and eosin. $\times 125$; reduced $\frac{1}{3}$.)

by, transformation to malignant squamous cells was noted; these cells could be seen to stream into the adjacent stroma in invasive character (Fig. 8). Careful examination of many sections proved that this case was not a "collision" type of tumor with separate basal and squamous cell carcinomas. Shortly after the biopsy examination, a one-stage radical vulvectomy with bilateral regional node dissection was performed; no node metastasis was demonstrated. The patient is currently alive and well without evidence of recurrence.

Diagnosis. The diagnosis was basal-squamous cell carcinoma of the vulva with stromal invasion by the squamous component.

Comment

These 4 cases illustrate the spectrum of histologic patterns which may occur in basal cell and basal-squamous cell carcinomas. They also serve to emphasize the marked difference in histology and the extremes of relative benignity and invasive malignancy which may be encountered in two sections of the same lesion. The importance of adequate excision and careful examination of multiple sections is obvious.

Treatment and prognosis

As with basal cell carcinomas in other locations, a variety of treatments have been

utilized, including electrocautery, carbon dioxide "snow," caustics, radium, and external irradiation⁵⁷; regarding surgical therapy, several authors recommend wide local excision^{4, 39, 60, 65} while others advocate unilateral vulvectomy,⁴⁸ wide complete vulvectomy,^{42, 50} or vulvectomy with regional node dissection.¹⁴

There are perhaps 20 cases of basal cell carcinoma of the skin reported in which it is alleged that a metastasis ensued with both the original growth and the metastasis being of pure basal cell type.^{12, 16, 28, 37, 49, 51} Some authors contend that there was an error in diagnosis⁵ or that, with large lesions, there was a direct extension to the nodes rather than lymphatic spread,⁴ while others state emphatically that practically all such metastatic tumors will be transitional or squamous cell in character when examined carefully.³⁴ It must be accepted, however, that basal cell carcinoma, especially long-standing lesions, may on rare occasions metastasize via the blood stream or lymphatics.

A number of basal cell carcinomas of the vulva have apparently been cured by irradiation.⁵⁷ Lamb,²⁷ however, noted that, in 20 years of experience with skin cancer, he had more difficulty with underirradiated, in-

filtrating basal cell lesions than with squamous cell carcinoma; others³⁴ have been impressed with the radioresistance of the basal-squamous cell lesions. Schrek⁴⁶ noted that recurrence of the basal cell type was "surprisingly high," 21.5 per cent, slightly higher than squamous cell carcinoma, 17.6 per cent, which he believes may possibly be related to the conservatism of surgeons and radiologists in treating basal cell lesions.

One of the 5 cases reported by Siegler and Greene⁴⁸ illustrates the potential difficulty which may be encountered with a basal cell lesion. A 49-year-old woman with a 3 cm. basal cell lesion on the fourchette received 4,200 r. by x-ray irradiation plus 1,200 mg. hr. of radium applied directly to the lesion. A recurrence one year later was treated by radical vulvectomy with removal of the posterior and lateral vaginal walls. An additional 4,000 r. was directed to the area 3 months later, and, one year following operation, extensive necrosis occurred. The patient died of wide local spread and infection; the autopsy showed no distant metastasis.

It should be emphasized that adequate serial examination must be performed on biopsy material of all suspected basal cell lesions to rule out a squamous component. As has been demonstrated by cases in this report, the finding of pure basal cells in one section does not preclude the possibility of basal-squamous cell lesions in another section. Because of possible multicentricity of origin and the marked propensity for local recurrence,⁵³ it is strongly recommended that a wide complete vulvectomy be performed for pure basal cell carcinoma. The total vulvectomy specimen must be examined by careful serial sections; if a significant squamous component is encountered, it is mandatory that a bilateral regional node dissection be added. If the original biopsy reveals a basal-squamous cell lesion, the treatment of choice is radical vulvectomy and bilateral regional node dissection as a one-stage procedure.

Concerning the prognosis, it is regrettable that the follow-up of only a small

number of basal cell carcinomas of the vulva, variously treated, has been reported. Wilson⁶⁵ found that in 17 cases reported in the literature up until 1941, 36 per cent of the patients died from carcinoma within 5 years after diagnosis. Smith and Pollock,⁵⁰ recommending complete vulvectomy for basal cell carcinoma, noted 3 of 5 patients alive 5 years later and another patient dead of unrelated cause. In Siegler and Greene's group of 5 basal cell lesions,⁴⁸ there were 2 postoperative deaths and one death within 2 years from recurrences after combined irradiation, radical vulvectomy, and partial vaginectomy. Folsome¹⁷ followed 2 patients for 4 and 6 years after "surgical excision" of basal cell carcinoma. The patient with pure basal cell carcinoma reported here has been followed for 7 months without recurrence. Two of the 3 patients with basal-squamous cell carcinoma reported here have been followed for 9 years and 6 years without recurrence; the third patient died of unrelated cause 6 years after operation.

Unfortunately, proper statistical evaluation of the prognosis of basal cell and basal-squamous cell carcinomas of the vulva is not possible because of the paucity of reported cases, the aforementioned frequent lack of follow-up, the difference of opinion concerning histologic classification, and the variety of treatments utilized. The sporadic reports, however, do seem to adjure the reader to be fully cognizant of the unpredictability of basal cell carcinoma of the vulva and suggest that one must approach this lesion with a higher regard and a more vigorous plan of therapy than are ordinarily accorded it, if the prognosis is to be improved.

Summary

1. Theories of histogenesis of basal cell and basal-squamous cell carcinomas of the vulva are discussed.

2. Approximately 80 cases of basal cell carcinoma of the vulva have been reported to date. The incidence of the pure basal cell type is calculated to be 2.7 per cent of all

vulvar malignancies; the incidence of the basal-squamous cell type is 2.5 per cent.

3. Clinical features and histologic characteristics are presented.

4. One basal cell and three basal-squamous cell carcinomas of the vulva are herein reported.

5. The importance of careful serial examination of suspected basal cell lesions to rule out a squamous component is stressed.

6. Wide complete vulvectomy is recommended for basal cell carcinoma, a lesion with a predilection for local recurrence as

well as a potential for multicentric origin and for transformation to basal-squamous cell carcinoma. A basal-squamous cell carcinoma must be treated by radical vulvectomy and bilateral regional node dissection.

I wish to express my appreciation to Dr. C. E. McLennan and Dr. E. C. Sandberg for their helpful reviews of this paper, to Dr. W. K. I. Manning for his aid in assembling histologic sections of vulvar carcinomas, to Dr. F. Norris and Dr. J. A. Spencer for permission to use a private case record, and to Mr. W. Renner for the photomicrographs.

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Evaluation of cytology as an aid in the prognosis of the treatment of cancer of the cervix uteri

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ATTEMPTS to predict the efficiency of various therapies for carcinoma of the cervix uteri have been the subject of a great deal of investigative work. One of the more promising methods described in recent years was that which seemed to allow for the recommendation of either radiation therapy or operation for the treatment of this form of malignant disease, based on the presence or absence of certain cytological changes in the nonmalignant basal or parabasal cells in smears obtained from women who had cancer of the cervix.^{1, 2}

If this method should prove successful in the hands of others then it would seem possible by means of a simple reproducible cytological examination to determine the type of therapy to be used for at least one form of malignant disease (already offering a real chance of early recognition by cytology) and, therefore, such determination of definitive therapy would help in reducing the mortality even further.

Vaginal and cervical smears are taken routinely on all women entering the Cancer Division of the Westfield State Sanatorium, and these smears were compared with conventional biopsy specimens and with the

tissues removed at operation. Since follow-up studies on patients treated by irradiation and patients treated with operation were readily available, an attempt was made to evaluate this diagnostic technique. Fourteen patients with cancer of the cervix in various stages were seen and, on the basis of cytological findings as suggested by Graham, therapy was instituted. In the patients treated by irradiation, smears were taken every second day for 2 weeks and biopsies 2 or 3 times during the 2 weeks following radiation. In the course of this procedure it was found that in a number of patients no cytological changes were seen in any of the basal or parabasal cells, and in other patients the number of basal or parabasal cells present in the smears were too few to allow for accurate interpretation.

Because of these discouraging results, it was decided to study the problem by use of a controlled series of patients and to evaluate all cases reported as positive in a cytology laboratory and which had been confirmed by conventional histological means. A total of 194 patients with carcinoma of the cervix uteri seen between 1945 and 1951 in the Cancer Division of the Westfield

From the Departments of Pathology of the Westfield State Sanatorium, Cancer Division, Westfield, Massachusetts; the Springfield Hospital, Springfield, Massachusetts; and the Springfield Cytology Laboratory, Springfield, Massachusetts.

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Table I

Stage 0 (carcinoma in situ)	17
Stage I	41
Stage II	85
Stage III	31
Stage IV	20
Total	194

State Sanatorium, all of whom were subjected to vaginal and/or cervical smear examination and all of whom had biopsy examinations performed, before definitive therapy was instituted, were studied.

The 194 patients were classified as outlined in Table I. Of these, 179 had epidermoid carcinoma, 13 had adenocarcinoma, and 2 had undifferentiated carcinoma.

One hundred and forty-seven patients were treated with radiation therapy in one form or another, 41 patients were treated by surgical intervention, and 6 were not treated. Seventeen patients received palliative external radiation, 119 had external x-ray treatment and implantation of radium, and 11 were subjected to the latter treatment plus lymphadenectomy. The forty-one patients treated by operation underwent procedures ranging from simple hysterectomy for carcinoma in situ to a Wertheim type of operation for invasive carcinoma.

Records of these patients treated between 1945 and 1951 were available for study, and the survey was started in 1957. It was, therefore, possible to review what had happened to these patients for at least 6 years. There were 57 patients (38.8 per cent) treated by irradiation who were alive and without evidence of disease from 6 to 12 years following the onset of the therapy.

Similarly, for the patients treated surgically, 29 (71 per cent) patients were alive and well from 6 to 12 years after operation.

In Table II the patients are grouped into the stages of the disease, therapy, and final outcome.

All 6 patients who had no treatment died from the disease within a period of 2 years. Twenty out of 28 patients with Stage III cancer who were treated radiologically and 2 out of 3 patients with Stage III cancer who were operated upon died of the disease. In this series, also, most patients with Stage III and Stage IV malignancies were treated by the Radiology Department.

Following this clinical survey, the cytology and the histology of the lesions in the 194 patients were reviewed. The cytological interpretations made on these patients from 1945 to 1951 were recorded as follows: 44 patients had negative smears; 27 patients had doubtful smears; and 123 patients had positive smears.

All smears were reviewed, and, of the 27 smears originally reported as doubtful, 24 were reclassified as positive while 5 of the smears originally reported as negative were reclassified as positive. There were no changes in the smears originally reported as positive.

All smears were screened for the presence or absence of basal or parabasal cells and

Table II

Stage	Total	X-ray and radium	Operation	No treatment	Patients still alive (more than 7 years)	
					X-ray	Operation
0	17	6	9	2*	3†/6	8/9‡
I	41	19	21	1	16/19	15/21
II	85	76	8	1§	30/76	5/8
III	31	28	3	0	8/28	1/3
IV	20	18	0	2	0/18	0/0
Total	194	147	41	6	57/147	29/41

*These 2 patients were not eligible for treatment in this hospital and were referred elsewhere; they were lost to follow-up. One of them was alive and well for 9 years without treatment (9833); no follow-up was available after that.

†One of these patients was well 4 years after treatment but was lost to further follow-up. The second patient died 4 years later of cerebral hemorrhage. The third patient died 2 years later of myocardial failure.

‡One patient had carcinoma of the rectum before the cancer of the cervix was recognized. She died of cancer of the rectum 3 years after panhysterectomy. No autopsy was performed.

§This patient had extensive carcinoma of the breast with metastases and carcinoma of the hand at the time the carcinoma of the cervix was diagnosed. She died one year later of the carcinoma of the breast.

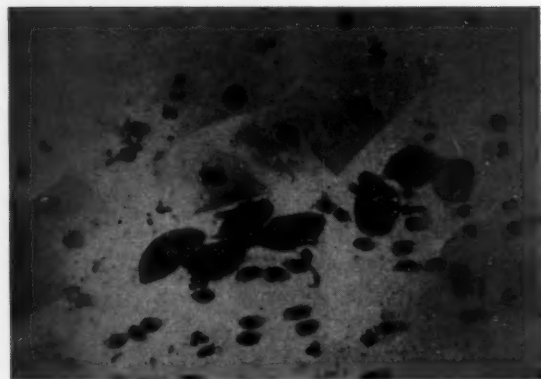


Fig. 1. Basal cells with finely vacuolated cytoplasm from 35-year-old woman without cancer.

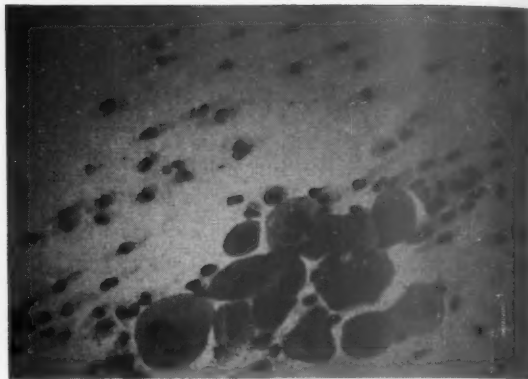


Fig. 2. Basal or parabasal cells, some with finely vacuolated and some with dense homogeneous cytoplasm.

recorded as follows: 66 smears showed no basal cells; 78 smears contained few; and 50 smears had many.

Allowing for difference in preparation of the smears, adequate fixation, staining, etc., two smears showed a fair number of basal cells which had a denser than usual cytoplasm and in which the cytoplasm was finely vacuolated, although the latter feature was also seen in the cornifying and even precornifying cells. Nine smears had few cells with such characteristics, and in 183 cases none could be found. Repeated examination of the smears was necessary to convince the examiners that the changes actually were present. This seemed to indicate that the cells with vacuolization or tinctorial characteristics which would set them apart from other cells in the gynecological smear actually occurred so rarely (in 11 out of 194 smears) that it would appear doubtful whether their presence had anything to do with the fact that the patient was suffering from cervical cancer.

The smears with the recognized cytological alterations were now plotted against the patients from whom they were taken, and it was found that the two smears which had frequent vacuolated basal and parabasal cells were taken from patients who had Stage II cancer of the cervix treated by operation. They were both over 50 years old and both were alive 7 years after operation without recurrence of disease. The 9

other smears in which some cytological changes were observable were correlated with the respective patients as follows:

Four were treated by irradiation and 5 were operated upon. No correlation could be found between the presence of the cytological changes in the basal or parabasal cells of these patients and the ultimate result of the therapy employed. Of these 9 patients, 6 were over 50 years old; one patient was 28, one was 43, and one was 44 years of age. Since it was not possible to find any interpretable cytological changes in the remaining 183 smears, no correlation between cytology and clinical approach of the patients was possible.

It is, of course, known that basal and/or parabasal cells occur more frequently in smears from patients at or after the menopause, and it was noted here that the cells with vacuolization and/or tinctorial difference were detected more readily in postmenopausal women.

Because this finding was thought to be more than fortuitous, 129 positive Class V smears collected over a period of 4½ years from patients with carcinoma in situ or invasive carcinoma were reviewed. In only 5 of these were cytological changes of significance observed, and all 5 patients were over 50 years old. As a final step, 1,000 consecutive diagnostic vaginal smears from the Cytology Laboratory were screened for the presence or absence of basal and/or

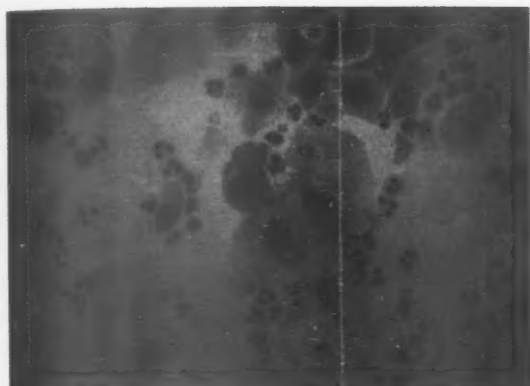


Fig. 3. Vacuolization of cytoplasm in basal cells and precornified cells. Same patient as in Fig. 1.

parabasal cells and the presence of cytological changes of significance in these cells. Basal and parabasal cells, as expected, were more numerous in women near or after the menopause and, where and when protoplasmic vacuolization or tinctorial changes of significance were observed, they were found in women of more advanced age, this regardless of whether or not the women had cancer of the cervix. There were 4 cases of unsuspected carcinoma in situ in these 1,000 smears. (In our cytology laboratory, the incidence of nonsuspected carcinoma in situ of the cervix discovered by vaginal smears is 0.5 per cent over a period of 5 years.)

Summary

In summary, therefore, the observations made here seem to indicate that in vaginal

and cervical smears one finds occasionally epithelial cells which have a denser than usual cytoplasm and which exhibit fine vacuolization. They may be recognized after some rather prolonged experience. While the changes may be observed in all epithelial cells present in the smear, they seem to be more numerous in cells interpreted as being basal or parabasal in origin. No attempt to determine the origin of these cells by use of conventional histological preparations has as yet been made. It is noteworthy that in this study they have been observed primarily in postmenopausal women, and it might be significant that they occurred in patients with cancer as well as in patients without cancer. In this study, their presence or absence bore no relationship to the results obtained by the various types of therapy employed for cancer of the cervix, and, therefore, their presence in the gynecological smear does not permit predetermination of the type of therapy to be used in any given patient.

The fact that cytological changes in the form of vacuolization or tinctorial density occurred more frequently in women of advancing age suggests that hormonal changes may be responsible for their appearance.

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Enzymatic débridement of cervical erosions

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CLASSICAL management of cervical erosions with chemical or electrocautery leaves much to be desired; truly ideal office management is yet to be achieved for this common problem. Toward this end, an evaluation of the effectiveness of an enzymatic débridement agent was undertaken.

Proteolytic enzymes have recently been employed as adjuncts in the treatment of a variety of human disorders. Conditions that had previously been considered to be slowly responsive to conventional therapy have been found to respond readily upon the addition of enzyme therapy.

Numerous enzyme preparations including streptokinase, streptodornase, and pancreatic derivatives, have been used alone and in various combinations, both parenterally and locally, in the treatment of chronic hemothorax, pulmonary abscess, and empyema,^{1, 11, 12} chronic bronchitis,⁷ chronic ulcer,^{3, 5, 8, 11} burns,^{2, 8} infected wounds and sinus tracts.^{6, 8, 9, 10} In general, therapy has resulted in hastened wound cleansing and healing, decreased necrosis, and over-all improved clinical courses.

Recent experimental studies and demonstrations of the clinical applicability of proteolytic enzymes have been extensively presented and reviewed.⁴ The rationale behind local therapy has been based on the

attack on insoluble fibrous proteins, fibrin, and desoxyribonucleoprotein. These proteins, constituents of pathological processes, may act to hinder tissue repair. Specific transformation of these substances into limpid solutions by the use of such enzymatic principles as desoxyribonuclease and fibrinolysin has resulted in decreased necrosis and accelerated wound healing. Although proteolytic enzymes have no specific bactericidal properties, bacteria have been eradicated by enhancing the action of antibodies, leukocytes, and antibiotics whose access is permitted into the area of infection and perhaps by the removal of substrates for bacterial proliferation.

Methods and materials

A controlled "double-blind" study of consecutive unselected postpartum patients with erosions of the cervix uteri was set up to attempt to evaluate objectively the agent in question.

Patients selected for this study were outpatients of the postpartum unit of Vanderbilt Clinic. All had been delivered 6 weeks earlier. They consisted of those consecutively discovered to have cervical erosions; they were channeled to a special unit set up specifically for the purpose of conducting the observations and treatments for this study.

Papanicolaou cytological studies were done routinely prior to therapy and were negative in all cases with one exception, that being in an instance of unsuspected intraepithelial carcinoma of the cervix. The obvious value of this precautionary measure is thus made clear.

From the Vanderbilt Clinic, Sloane Hospital for Women, Columbia-Presbyterian Medical Center, the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons.

Having secured the patient's written permission, we obtained pretreatment photographs of the cervical lesion. These were taken with an Exa single-lens reflex camera with close-up lens systems and built-in circle flash component.* Photographs were obtained at each subsequent visit until the conclusion of observations. All were labeled with consecutive numbers applied against the posterior fornix of the vagina by means of disposable tongue depressors at the distal ends of which were glued small, appropriately numbered tabs.

Three distinct phases of the study were carried out separately. After a short initial pilot study which tended to show that the material was probably effective (the pilot study is not reported herewith), the second phase was embarked upon, namely, the testing of freshly prepared solutions of stable gelsiccated material. Unknown to the investigators, three preparations identified only by code designations were evaluated: a placebo (I) of the same pH and constitution (excluding enzymes) as the other solutions; a combination of bovine serum fibrinolysin, 33 units, and purified bovine pancreatic desoxyribonuclease, 12,400 units, (II); and a combination of fibrinolysin, 63 units, and desoxyribonuclease, 38,600 units, (III). Patients were assigned to the several groups in consecutive order, without selection. The material was freshly prepared just prior to administration by the addition of 10 ml. sterile saline to the dry powder. The solution was applied directly onto the cervix by means of a blunt cannula; a gauze tampon was placed against the cervix to aid in the retention of the fluid. Instructions were given for the patient to remove the tampon the following day; no douching was to be performed. The patient was to return at weekly intervals for similar treatments for a maximum of four such visits, at which time photographs were also obtained. At the conclusion of the series of visits, an over-all clinical estimate was made of the effectiveness, and those erosions requiring it were cau-

terized according to standard current therapy.

It was anticipated that the photographs could be so evaluated that the actual area of erosion could be measured (from camera lucida drawings and planimeter measurements of the relative areas of involvement), but it soon became evident that the lesions do not shrink at a measurable rate from the margins, but that islands of epithelium arise within the confines of the lesion, obscuring accurate measurement of the rate of healing. Accordingly, objective estimations were sought from the photographically recorded changes. Four categories were easily differentiated: healed, improved, unchanged, and worse.

Three independent observers graded the results in unidentified photographs, grouped only by the patient-sequence, according to the degree of involvement and, more pertinently, to the effectiveness of therapy. It is important to emphasize that the mode of therapy as well as the code designations were completely unknown to these observers.

The final phase of the study concerned the evaluation of ointment preparations for self-administration by the patient. Four were made available: a placebo (IV), an ointment containing 10 units fibrinolysin and 6,000 units desoxyribonuclease per half ounce (V), and one containing 25 units fibrinolysin and 15,000 units desoxyribonuclease per half ounce (VII). The same initial procedures were carried out in this series. The ointment was administered at the initial visit and the patient instructed in its nightly use. A 2 ounce supply, with appropriate applicators, was given to the patient. No tampons were used; douching was not permitted. The patient was told to return in 3 weeks. No other follow-up visits were made in this group except as might be required for cautery, if performed. "Before" and "after" photographs were obtained. Evaluation was carried out in much the same manner as in the first group.

Results

The first major group consisted of 115 patients accepted for treatment, of whom

*Manufactured by the Medical-Dental Photographic Supply Company, Levittown, New York.

38 received the placebo preparation (solution I), 37 solution II, and 40 solution III. Ten never returned; 7 others returned only once more. These 17 were excluded from the study because of inadequate follow-up. Over-all loss to follow-up was 14.8 per cent (only 62 per cent returned for the full series). The remaining 98 (those who were seen at least 3 times) were carefully evaluated, and included 33, 33, and 32 in the respective subgroups.

The groups were rather well matched in so far as age (averages 25.7, 25.1, and 24.8, respectively), parity (2.2, 2.0, and 2.1), and frequency of complications of labor and delivery.

In all, 296 courses of treatment were ad-

ministered. "Blind" objective evaluation of these cases failed to reveal any statistically significant differences between the 3 courses of therapy. The success rate, based on obvious healing as seen in the photographs (in which there was complete agreement by all observers) was 13 of 33, or 39.4 per cent, in the placebo group (I), 15 among 33, or 45.5 per cent, after solution II treatment, and 12 of 32, or 37.4 per cent, after solution III.

Subjective clinical evaluation, based largely on the gross appearance of the lesion at the last visit, yielded success rates (sufficient healing to negate further treatment) of 45.5, 39.4, and 46.8 per cent, respectively. It is apparent that, in the dosage schedule used

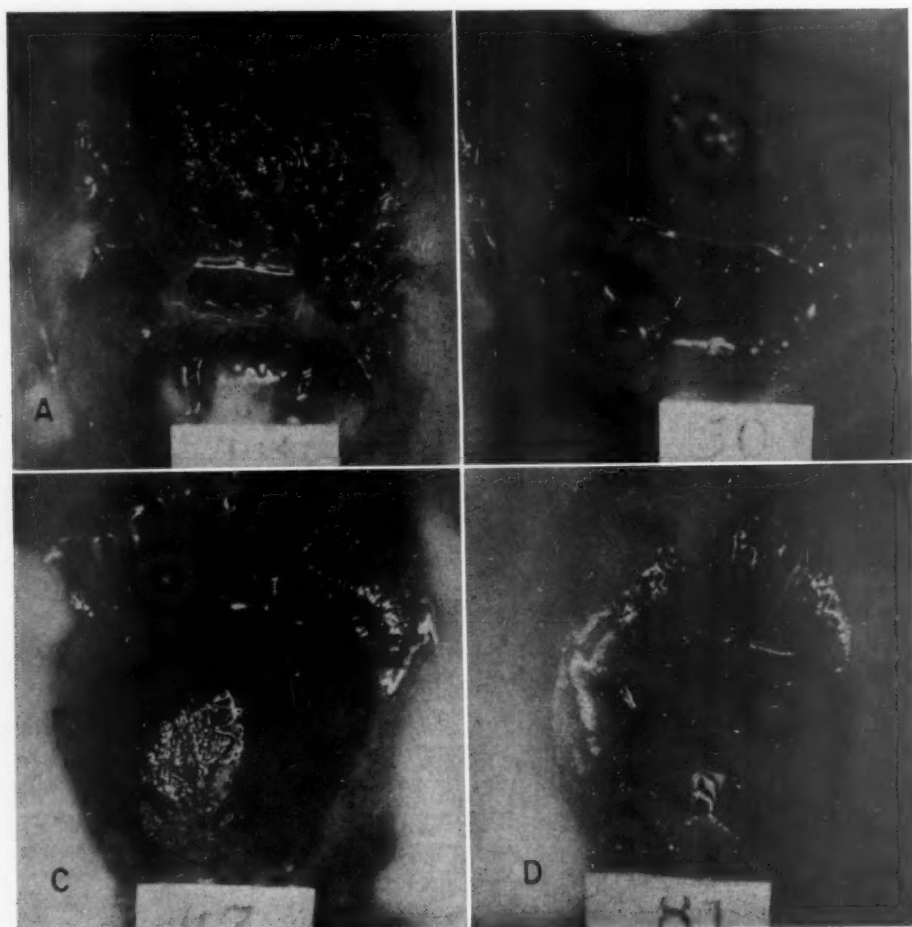


Fig. 1. Effect of enzymatic débridement of puerperal cervical erosion, A, prior to treatment; B, same case 3 weeks later following course of ointment V; C, prior to treatment; and D, after treatment with preparation VII.

(one application at weekly intervals), there was no improvement over that of the control.

The second group consisted of 48 patients, 12 in each subgroup. All kept their follow-up appointments. Clearly, this method of therapy found greater patient acceptance. In most cases the self-treatment lasted 7 days. The four groups were comparably constituted with regard to such factors as age, parity, methods of delivery, fetal positions and weights, and complications of labor and delivery.

Clinical determination of complete healing, requiring no further care, occurred in one (8.3 per cent) in group IV (placebo), 3 (25.0 per cent) in the group treated with ointment V, 4 (33.3 per cent) after ointment VI, and 5 (41.7 per cent) after preparation VII. Inclusion of cases deemed to have undergone "marked healing" changes these data to one in the placebo group (still 8.3 per cent), 7 (58.3 per cent) each in groups V and VII, and 6 (50.0 per cent) in group VI.

"Blind" photographic estimations revealed agreement on the criteria for healing (Fig. 1) among the placebo ointment (IV) group in 2 (16.7 per cent), in 5 in the ointment V group (41.7 per cent), and in 6 each in the other two groups (50 per cent). When the data were expanded to include cases with documented marked improvement following the single course of treatment, three "successes" were found in the control group (25.0 per cent), 6 (50.0 per cent) in group V, 7 (58.3 per cent) in group VI, and 8 (66.7 per cent) in group VII.

Evaluation on an arbitrary scale of -1 for an erosion which becomes worse under observation, zero for no change, +1 for moderate healing, and +2 for complete healing, with three observers evaluating two sets of unidentified duplicate photographs for each case (allowing a maximum score for any one case of +12), gives one a scoring system for purposes of semiquantitative objectivity. Of a maximum score of +144 for any group of 12 individuals, the placebo group (IV) attained +19; the patients receiving the combination of 10 units fibrinolysin and 6,000

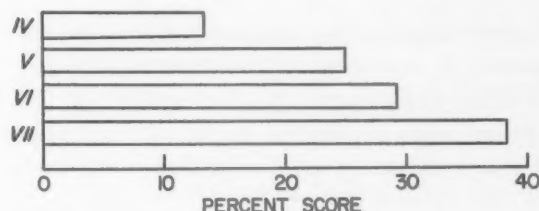


Fig. 2. Horizontal axis refers to per cent of cervical erosion response on an arbitrary scoring system (see text). Vertical references are to the several ointments evaluated: IV, placebo; V, fibrinolysin, 10 units, and desoxyribonuclease, 6,000 units; VI, same plus 1 per cent chloromycetin; VII, fibrinolysin, 25 units, and desoxyribonuclease, 15,000 units.

desoxyribonuclease (V) +36, those receiving the ointment containing Chloromycetin (VI) +42, and those who received 25 units fibrinolysin and 15,000 desoxyribonuclease per half ounce ointment (VII) +55. On a percentage basis (Fig. 2) the scores were 13.2, 25.0, 29.2, and 38.2 per cent, respectively. This checks closely with the less critical qualitative estimates cited above.

Statistical analyses of these latter data tend to confirm the clinical impression of effectiveness. Analysis of the nonobjective clinical evaluations (chi-square) revealed significant differences between treated and untreated groups ($\chi^2 = 8.6$, $P = 0.004$); the objective evaluations lent support but not immutable proof to this contention ($\chi^2 = 4.6$, $P = 0.03$). Trends, however, seemed clear-cut. Uniform progression of results from the control through the weaker preparations to the stronger is impressive (Fig. 2) and may indeed form the basis of a dose-response relationship, although the numbers of cases involved do not warrant this refinement.

In no instance in the entire study was there any evidence of adverse reaction due to the medications administered.

Comment

The study herein reported has attempted an essentially objective evaluation of the effectiveness of enzyme preparations in the nonsurgical treatment of erosions of the cervix in a truly "double-blind" fashion.

Several important matters were made apparent. It was seen, for example, that purely clinical evaluations of the status of an erosion were of limited value. Many lesions deemed clinically to be healed were seen by the unbiased sharp eye of the camera to require further care; others thought to need cauterization were seen to be essentially completely epithelized by myriad islets of epithelium. It was obvious that for true objectivity a scheme was needed whereby neither those treating the patients nor those evaluating the results (as depicted photographically) would know the identity of the material used, and, among those evaluating the end results, which of the several unknown preparations had been used in any of the cases. This has been accomplished.

The necessity for cytological study as a screening method is stressed even in the presence of the most benign-appearing erosions. The single instance of intraepithelial carcinoma detected in this series serves to illustrate this point and to reiterate the essential need for such an investigation prior to the initiation of any form of therapy.

As regards the value of enzymatic débride-ment agents—in this instance, the several combinations of fibrinolysin and desoxyribo-nuclease—in the treatment of cervical erosions there seems little doubt. The limitations of usefulness appear to take shape. An inadequate treatment schedule, for example, may account for the poor results obtained in the groups in which freshly prepared solutions were used. In these cases two or three single treatments at weekly intervals were obviously insufficient and the data obtained unworthy of interpretation. This modality of treatment, however, required administration by the physician, and even weekly visits by the patient were difficult to maintain as

evidenced by the high loss to follow-up.

The introduction of an ointment preparation for self-medication by the patient averted this problem. Patients were seen prior to treatment and then 3 weeks later for evaluation. The 100 per cent follow-up is an indication of its acceptance; the data indicate its effectiveness in the dosage schedule of nightly administration for about a week (approximately $\frac{1}{4}$ ounce per treatment).

The preparation containing 1 per cent Chloromycetin (VI) did not appear to effect significantly better results than its counterpart (V) which contained equal concentrations of enzymes but was devoid of antibiotic. Nevertheless, further study would be necessary to prove this contention, particularly since the weight of data seems to lean, albeit slightly, toward an enhancing effect.

Conclusions and summary

Objective evaluation of the healing effects on puerperal cervical erosions brought about by the enzyme combination of fibrinolysin and desoxyribonuclease has yielded evidence to suggest positive action.

Better patient acceptance, efficacy, and ease of application favor the use of an ointment preparation.

The addition of a broad-spectrum antibiotic to the enzyme combination did not seem to augment its value to any significant degree.

The need for cytological investigation of cervical erosions prior to the initiation of any form of therapy is stressed.

The fibrinolysin-desoxyribonuclease preparations used in this study were supplied by Parke, Davis & Company, Detroit, Michigan, whose generous support is herewith gratefully acknowledged.

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Cervicectomy following supravaginal hysterectomy

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THIS presentation is a survey of all the patients who were subjected to cervicectomy following supravaginal hysterectomy during the 10 year period, 1948-1957, at the Pennsylvania Hospital, Philadelphia.

Since supravaginal hysterectomy was more of a routine procedure in the past, it has subsequently presented the problem of the retained uterine cervix to the gynecologist. At present, supravaginal hysterectomy is resorted to only in complicated or unusual cases or in the face of anesthetic difficulties.

A total of 35 patients were included in this study; 30 were multiparas and 5, nulliparas. Among these 5, one was single and hence an absolute nullipara; the other 4 were infertility patients.

Table I shows the admission diagnosis prior to supravaginal hysterectomy. There were 16 patients who had leiomyoma uteri. There were 8 patients in whom the diagnosis was "unknown" since they were operated on in hospitals other than the Pennsylvania Hospital, and their records were not available at the time of cervicectomy. Three patients were operated on for "dysfunctional uterine bleeding." Three other patients claimed they had a "tumor of the womb" prior to hysterectomy (probably leiomyoma uteri). One patient who was operated on for pelvic endometriosis was found to have an "adenocanthoma of the fundus uteri." Two years later she had vaginal cervicectomy performed because of

prolapse of the cervical stump. The cervical specimen was normal. This patient has survived 5 years following the discovery of adenocanthoma of the fundus uteri without a recurrence of malignancy. Table I shows the high incidence of leiomyoma uteri among the candidates for hysterectomy.

The indications for supravaginal hysterectomy in this series were as follows: In 23 patients this operation was performed as a "routine" procedure. There were 2 patients with pelvic adhesions and one with anesthetic complications which required supravaginal hysterectomy. There were 9 cases in which the indications for this procedure could not be determined since hysterectomy had been performed in other hospitals. These cases were labeled as "unknown."

Table II presents the chief complaints for which the patients sought medical advice following hysterectomy. There were 11 patients whose chief complaint was vaginal

Table I. Diagnosis prior to supravaginal hysterectomy

Diagnosis	No. of patients
Leiomyoma uteri	16
Unknown	8
Dysfunctional uterine bleeding	3
"Tumor of the womb"	3
Pelvic inflammatory disease	2
Cystic ovaries	1
Primary dysmenorrhea and uterine retroversion	1
Pelvic endometriosis	1
Total	35

From the Pennsylvania Hospital.

spotting. Likewise, there were 11 patients whose chief complaint was "a mass at the introitus" (cervical prolapse). Two patients, during routine pelvic check-ups, had Papanicolaou smears done which showed "suspicious tumor cells." Biopsies of these two cervixes were positive for epidermoid carcinoma of the cervix, in situ and Stage I, respectively. There was also a cervical myoma discovered on routine pelvic examination of another patient. It is interesting to note that the other 2 patients in this series who had cervical carcinoma presented the chief complaint of vaginal spotting. The patient with cervical leiomyosarcoma complained of leukorrhea and a mass protruding at the introitus.

The indications for cervicectomy are listed in Table III. There were 4 patients operated on for cervical malignancy. Two had epidermoid carcinoma in situ of the cervix; one had epidermoid carcinoma, Stage I. The fourth patient had a leiomyosarcoma of the cervix. There were 13 patients who had chronic cervicitis; malignancy had to be ruled out in 7 of these patients. As has been mentioned, there were 11 patients with the chief complaint of cervical prolapse. Actually, this diagnosis was correct in only 9 cases since one patient had a pedunculated leiomyosarcoma of the cervix, and another had a degenerated,

Table III. Indications for cervicectomy

Indications	No. of patients
Epidermoid carcinoma in situ, cervix	2
Epidermoid carcinoma, Stage I, cervix	1
Leiomyosarcoma of cervix	1
Prolapsed cervical stump	8
Prolapsed cervical stump with polyp	1
Chronic cervicitis, rule out malignancy	7
Chronic cervicitis	2
Cystoectocoele	5
Ovarian cyst and chronic cervicitis	4
Ovarian cyst	2
Degenerated, pedunculated cervical myoma	1
Endometriosis uterosacral area, left	1
Total	35

pedunculated cervical myoma. One patient was operated on for cervicitis but turned out to have "adenocarcinoma, Grade III, of the cervix." There were 31 patients operated on with a preoperative diagnosis of benign disease. Among these, one patient had adenocarcinoma, Grade III. The symptoms in these 31 patients were of sufficient degree to convince both the patient and the gynecologist that cervicectomy was indicated.

The operative approach of cervicectomy in these patients was through the vaginal and abdominal routes. There were 23 done through the vaginal route and 12 through the abdominal route. The abdominal approach was employed for patients with adnexal masses or with known retained ovaries and for patients with cervical malignancy, except for one case. This exception was a patient with epidermoid carcinoma in situ of the cervix, who was known to have had bilateral salpingo-oophorectomy during hysterectomy. The gynecologists had one thing in common, and that was that they did not spare any ovary. They did unilateral or bilateral salpingo-oophorectomy together with cervicectomy through the abdominal approach. Five ovarian cysts were excised; none of these was malignant. It is evident that the vaginal approach to cervicectomy was employed in this series whenever feasible. The advantage of the vaginal approach is that it makes opening of the peritoneal cavity unnecessary and enables the correction of cystocele and rectocele.

Table II. Chief complaint post hysterectomy for which patients sought medical advice

Chief complaints	No. of patients
Vaginal spotting with	11
(a) Erosion	9
(b) Clean cervix	2
Mass at introitus (cervical prolapse)	11
(a) Per se	6
(b) With leukorrhea	1
(c) With vaginal spotting	1
(d) With stress incontinence	3
Lower abdominal pain	5
Backache and involuntary incontinence	4
Backache and weight loss	1
Referred with suspicious Papanicolaou smears	2
Referred with cervical myoma	1
Total	35

A comparison between cervical biopsy and Papanicolaou smear findings in this series was done. There were only 11 patients who had Papanicolaou smears taken prior to cervicectomy. Where cervical biopsy revealed malignancy, the Papanicolaou smear results were as follows: none was "positive"; two were "suspicious" for tumor cells (one of them twice), and one was "negative." In the benign group, one patient had a "positive" smear (two times), and seven other patients had "negative" smears. The above comparison between cervical biopsy and Papanicolaou smear indicates that the Papanicolaou smear was not a sufficient criterion on which to base a diagnosis, even if correlated with the clinical findings.

Table IV. Time interval between operations and subsequent diagnosis of malignancy

<i>Time interval</i>	<i>Patients subjected to supravaginal hysterectomy and cervicectomy</i>	<i>Patients in whom malignancy developed</i>
0-6 months	1	1
7 months-2 years	2	1
3- 5 years	5	1
6-10 years	12	1
11-20 years	13	1
21-30 years	2	0
Total	35	5

Table IV shows the time interval from supravaginal hysterectomy to cervicectomy. One patient had cervicectomy 6 months after supravaginal hysterectomy for what was diagnosed as "epidermoid carcinoma in situ, of cervix." This table shows an increased incidence of cervicectomy as the time interval following supravaginal hysterectomy increased. The retained uterine cervix is potentially pathological and may necessitate excision many years after hysterectomy.

Table IV also shows that 2 patients developed cervical stump carcinoma 6 months and 2 years following supravaginal hysterectomy, respectively. Cosbie⁴ states that if carcinoma develops within 3 years follow-

ing supravaginal hysterectomy, the carcinoma was present and demonstrable at the time of operation. He classifies it as "coincidental" carcinoma. Ward⁹ is of the opinion that if carcinoma develops clinically within one year of operation the lesion is "coincidental." Hahn⁶ defines a "coincidental" carcinoma as one occurring within 2 years of the original hysterectomy.

In this series, there were a total of 5 cervical malignancies. One case was an epidermoid carcinoma in situ of the cervix discovered 6 months after hysterectomy. The second case was a leiomyosarcoma of the cervix discovered exactly 2 years after hysterectomy. The other 3 cases of carcinoma are classified as "sequential" carcinoma since they occurred over 2 years after hysterectomy. One patient had epidermoid carcinoma in situ exactly 3 years following hysterectomy. A second patient had epidermoid carcinoma, Stage I, of the cervix 9 years after hysterectomy. The third "sequential" case was discovered to be adenocarcinoma, Grade III, of the cervix when cervicectomy was performed 20 years after hysterectomy. Hence, the time interval between the original operation and the discovery of cervical stump malignancy varied from 6 months to 20 years, averaging 8 years.

Table V. Age of patients at operation and subsequent diagnosis of malignancy

<i>Age (years)</i>	<i>Total No. of patients</i>		
	<i>Hysterectomy</i>	<i>Cervicectomy</i>	<i>Malignancy</i>
21-30	6	1	1
31-40	17	4	1
41-50	9	16	2
51-60	3	10	1
61-65	0	4	0
Total	35	35	5

Table V shows that there were 17 patients belonging to the 31-40 age group at the time of hysterectomy. There were 16 patients belonging to the 41-50 age group,

and 10 patients in the 51-60 age group at the time of cervicectomy. The 5 malignant cases were diagnosed at 30, 36, 42, 45, and 53 years, respectively. Hence, there was no significant relationship between the patients' ages and the development of cervical malignancy.

Table VI. Pathological diagnosis of cervical stumps

Pathological diagnosis	No. of cases
Epidermoid carcinoma in situ	1
Adenocarcinoma, Grade III	1
Chronic cervicitis with Nabothian cysts	13
Chronic endocervicitis	5
Chronic cervicitis and squamous cell metaplasia	4
Leiomyoma cervix	2
Normal cervix	2
Chronic cervicitis and parovarian cyst	2
Chronic cervicitis and corpus luteum cyst	1
Chronic cervicitis and Leydig cell rest cyst	1
Chronic cervicitis and urethral caruncle	1
Chronic cervicitis and chronic salpingo-oophoritis	1
Chronic endocervicitis and serous cystoma	1
Total	35

The most common pathological diagnosis was "chronic cervicitis," which occurred in 13 patients. There were 6 cases of chronic cervicitis associated with ovarian cysts, etc. In addition, 4 cases were reported as chronic cervicitis with squamous cell metaplasia, making a grand total of 23 cases of chronic cervicitis. There were 6 cases of chronic endocervicitis, and 2 cases of cervical leiomyoma. Two patients with cervical stump prolapse and cystocele were reported to have normal cervixes pathologically. In this tabulation, there are only 2 cases of malignancy. The other 3 cases of malignancy in this study were diagnosed by biopsy but did not show the malignant lesion in the specimen obtained by cervicectomy. The pathologist claimed the malignant lesions had been excised *in toto* during biopsy in each of the 3 cases. The above histopathological diagnoses show that the most common lesion of the retained uterine cervix in this study was "chronic cervicitis"

with or without "cervical prolapse."

The complications following cervicectomy were reviewed. Urinary retention, complete, occurred in 5 patients. There were 4 cases of mild cystitis and one case of cystitis with fecal impaction. The most serious complication was that of urinary bladder perforation during abdominal cervicectomy. This patient developed cystitis despite antibiotic therapy. Another patient developed thrombophlebitis in the left leg. There was also one patient who developed bleeding from the vaginal cuff 2 weeks after cervicectomy.

Comment

This study included a total of 35 patients in whom cervicectomy was performed following supravaginal hysterectomy. There were 16 patients in whom the indication for hysterectomy was leiomyoma uteri. In 23 patients subjected to supravaginal hysterectomy, the operation was performed as a routine procedure.

Total hysterectomy has been advocated as the procedure of choice for over 30 years in patients in which hysterectomy is indicated.^{1, 3, 5} In the cases in which it is not possible to remove the cervix, thorough curettage of the cervical canal and conization of the external os should be performed to denude these zones of all epithelium.² Masson⁸ pointed out that this does not eliminate the danger of the subsequent development of carcinoma from the squamous epithelium of the portio that remains. Supravaginal hysterectomy often gives the patient a false sense of security, and it is the responsibility of the surgeon to inform the patient that the cervix was left in place. The patient should report periodically for routine pelvic check-ups, and cytological studies should be done every 6 months. Cervical biopsy should be performed in patients with cervical lesions or in the presence of symptoms. A combined incidence of 7 to 8 per cent of stump carcinoma together with a steady decline in mortality and morbidity associated with total hysterectomy makes this operation mandatory today.⁵

An increased incidence of cervicectomy as the time interval following supravaginal hysterectomy increases is shown in this series. The time interval between the original operation and the discovery of cervical stump malignancy varied from 6 months to 20 years, averaging 8 years. In this series, the highest incidence of hysterectomies occurred in the 31-40 age group. Likewise, the highest incidence of cervicectomies occurred in the 41-50 age group. There was no significant relationship between the patients' ages and the development of cervical malignancy. Among the patients with cervical malignancy, the youngest was 30 years old and the oldest was 53. "Coincidental" carcinoma of the cervix is here defined as that occurring within 2 years after supravaginal hysterectomy; there were 2 such cases in this series.

The chief complaint was vaginal spotting or cervical prolapse in 63 per cent of the cases. These two symptoms were responsible for a great deal of anxiety on the part of the patient as well as the gynecologist. Likewise, these symptoms convinced both patient and gynecologist that cervicectomy was indicated.

The most common indication for cervicectomy was chronic cervicitis. There were 13 patients operated on for this condition; among these there were 7 patients in which malignancy was suspected. The second most common indication for cervicectomy was cervical prolapse. The corrected number of patients with this condition was 9. Four patients were operated on for cervical malignancy.

Vaginal cervicectomy was done in 23 patients. It was the route of choice whenever possible, permitting the repair of cystocele and rectocele. Abdominal cervicectomy was employed in 12 patients for the reasons already mentioned.

In this series, Papanicolaou smears were done in 11 patients prior to cervicectomy. These patients also had cervical biopsies. Among the patients in whom biopsy specimens proved to be benign, there were 7 with negative Papanicolaou smears. One patient

had a positive Papanicolaou smear twice.

Three patients had positive biopsies for malignancy; none of these patients' Papanicolaou smears were reported as positive. Two patients had "suspicious" smears, and one patient had a negative smear. Cervical biopsy of one of the patients with a suspicious Papanicolaou smear revealed an epidermoid carcinoma, Stage I. The second patient with a suspicious Papanicolaou smear was proved to have epidermoid carcinoma in situ by biopsy. One patient with a negative smear had a biopsy positive for epidermoid carcinoma in situ. There was one other patient whose Papanicolaou smear was negative but who later was proved to have cervical malignancy. The pathological diagnosis was adenocarcinoma, Grade III, of the cervix. Cervical biopsy is of the utmost importance in establishing the diagnosis prior to cervicectomy.

Chronic cervicitis with or without cervical prolapse was present in 23 (66 per cent) of the patients in this series. There were 5 patients with ovarian cysts, but none was malignant. Histopathological study of the cervical stumps revealed only 2 cases of carcinoma. Two other cases of carcinoma and one of leiomyosarcoma diagnosed previously by biopsy proved to be chronic cervicitis after cervicectomy. The malignant lesions had been excised *in toto* by biopsy.

The incidence of cervical malignancy in this series of 35 patients was 14.3 per cent. Since one case was a leiomyosarcoma, the incidence of carcinoma of the cervical stump was 11.4 per cent. It is interesting to note that during the 10 year period, 1948-1957, there were 322 cases of cervical carcinoma treated at the Pennsylvania Hospital. Hence, 1.2 per cent of the cervical carcinomas occurred in patients with retained uterine cervixes. The employment of total hysterectomy as a routine procedure, whenever possible, would eliminate all the anxiety and risks which patients with retained cervixes face when subjected to a second operation. Irwin⁷ reported that 5 per cent of cervical carcinoma occurs in patients with cervical stumps.

Summary

1. A total of 35 patients with previous supravaginal hysterectomy subjected to cervicectomy during the 10 year period, 1948-1957, were reviewed.

2. In 23 (66 per cent) patients, the supravaginal hysterectomy was performed as a routine procedure. Leiomyoma uteri was the most common indication for hysterectomy. The responsibility of the gynecologist in following up the patients with retained uterine cervixes and the importance of performing total hysterectomy are stressed.

3. The time interval between the supravaginal hysterectomy and the discovery of malignancy of the cervical stump varied from 6 months to 20 years, averaging 8 years. Hence, there is no "age limit" with regard to cervicectomy. Patients with cervical stumps may necessitate cervicectomy at any age.

4. Vaginal spotting and cervical prolapse were the two most common symptoms and convinced both the patient and the gynecologist that cervicectomy was indicated.

5. Chronic cervicitis was the most frequent pathological finding. There were 13 such cases. Malignancy was suspected in 7 cases, and among these one proved to be an adenocarcinoma, Grade III. Four patients with biopsies positive for malignancy were subjected to cervicectomy.

6. Vaginal cervicectomy was done in 23

(66 per cent) cases; the abdominal route was employed in 12 cases.

7. There was no satisfactory correlation between the Papanicolaou smears and cervical biopsies. This study shows that in the presence of signs or symptoms pertaining to the retained cervix, a cervical biopsy is imperative to establish the diagnosis.

8. Chronic cervicitis with or without prolapse of the stump was found in 63 per cent of patients. There were 5 cases of cervical malignancy. Two patients had epidermoid carcinoma in situ; one patient had epidermoid carcinoma, Stage I. A fourth patient had an adenocarcinoma, Grade III. The fifth patient had a leiomyosarcoma of the cervix, but it was not a recurrence. The pathological diagnosis after hysterectomy was leiomyoma uteri.

9. The most common postcervicectomy complications were those of the urinary bladder.

10. The incidence of cervical malignancy in this series of 35 women with retained uterine cervixes was 14.3 per cent. In this series, the incidence of carcinoma of the cervical stump was 11.4 per cent. Among the 322 patients treated for cervical carcinoma during the 10 year period, 1948-1957, there were 4 cases which developed in cervical stumps. This gives an incidence of 1.2 per cent for cervical stump carcinoma in this series.

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Genital tuberculosis in women

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IN RECENT years there has been a widespread awakening of interest in the whole subject of genital tuberculosis in women and particularly in endometrial tuberculosis. It is now generally realized that this condition is much more frequent, in Britain at least, than was previously thought, and it is likely that this is due in great part to the routine use of endometrial biopsy or diagnostic curettage in patients with infertility, irregular uterine bleeding, or amenorrhea. Although definite proof is usually lacking, it is probable that the Fallopian tubes are involved in the vast majority of cases of endometrial infection.

Incidence

Very varied views have been expressed on the question of the incidence of endometrial tuberculosis. In an attempt to clarify this point, the matter was studied from a number of aspects; the results are shown in Table I. The first aspect is from the accumulated histological material of a gynecological hospital. Some years ago, a study was made of the histological preparations of the Pathological Department of the Royal Samaritan Hospital for Women over a period of 7 years.² During this time, 5,521 curettings and 864 uterine specimens were examined histologically. Tuberculosis of the endometrium was found 71 times (1.1 per cent).

From the David Elder Infirmary.

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The next aspect is from the clinical records of a gynecological hospital. A study was made of the clinical records of the Royal Samaritan Hospital for Women, during a 20 year period.¹² During this time, 65,943 gynecological patients were admitted to the hospital and histologically proved genital tuberculosis of various types was discovered in 369 instances (0.56 per cent). Tuberculosis of the endometrium was found in 178 cases, representing 48.19 per cent of cases of genital tuberculosis and 0.27 per cent of all admissions to the hospital.

The next aspect is the incidence of tuberculosis of the endometrium in infertility. During a 20 year period ending on Dec. 31, 1954, Sharman¹ investigated 3,804 cases of primary infertility in the Royal Samaritan Hospital for Women. In all of these patients endometrial biopsy or curettage was carried out, endometrial tuberculosis being found in 216 (5.6 per cent). In recent years, many similar though usually much smaller series have been published throughout the world. The figures reported vary considerably, and

Table I. The percentage incidence of tuberculosis of the endometrium in Glasgow

Histological material of a gynecological hospital	1.1 %
Clinical records of a gynecological hospital	0.27%
Infertility	5.6 %
"Functional uterine bleeding" between puberty and the menopause	1.0 %
"Functional uterine bleeding" in young women	4.0 %
"Organic uterine bleeding"	0.9 %
Postmenopausal bleeding	0.1 %

many are appreciably higher than the 5.6 per cent found by Sharman.¹ There is certainly nothing in these figures or in the others quoted previously to suggest that genital tuberculosis in women is unusually frequent in the West of Scotland.

The last aspect is the incidence of endometrial tuberculosis in various types of abnormal uterine bleeding. This matter has been investigated in four groups of cases. The first of these is functional (or dysfunctional) uterine bleeding occurring between puberty and the menopause. The endometrium was studied histologically in 1,000 cases of abnormal uterine bleeding occurring in the absence of gross pelvic pathology, all types of abortion and all patients with bleeding after the menopause being excluded.³ Tuberculosis of the endometrium was found on 10 occasions (1 per cent).

The second is abnormal uterine bleeding in young patients. A histological study was made of the endometrium in 200 cases of abnormal uterine bleeding occurring in women aged 20 years or under.⁶ Endometrial tuberculosis was found in 8 cases (4 per cent). It is considered that this incidence constitutes a clear-cut indication for curettage in such patients, all other considerations apart. The value of early diagnosis and treatment in young patients with genital tuberculosis is obvious, and this may improve the prospects of cure before the tubes are damaged beyond recovery.

The third group consists of cases of uterine bleeding with a possible organic pelvic cause. The endometrium was studied histologically in 1,000 cases of abnormal uterine bleeding occurring in association with gross pelvic disease which might explain it.⁴ All patients with postmenopausal bleeding and all types of abortion were excluded from this series. Tuberculosis of the endometrium was found 9 times (0.9 per cent).

The fourth group consists of cases of postmenopausal bleeding. An analysis was made of 1,000 cases of postmenopausal bleeding, special attention being paid to the histological condition of the endometrium.¹³ Tuberculosis of the endometrium was found only

once (0.1 per cent). Menopause had occurred 19 years previously in the 46-year-old patient.

Clinical aspects

The present series consists of 325 cases of this condition which have been investigated in Glasgow during the past 9 years. A few of these patients were encountered in the routine work of my unit and a considerably larger number were referred from other gynecological departments and chest clinics throughout the West of Scotland. About 40 new cases are now seen each year. For several years I have held a weekly clinic devoted entirely to genital tuberculosis in women. In the initial stages, the number of patients attending was small, but today the average weekly attendance is about 12 patients.

Previous health. A careful inquiry was made into the previous history of all patients, particularly in relation to earlier extragenital tuberculous lesions. A history of definite or possible extragenital tuberculosis was obtained in 177 of the 325 patients. Details of these illnesses are shown in Table II.

It will be seen that the total number of lesions is 214; this is due to the fact that multiple conditions had been present in quite a number. The interval between the earlier tuberculous manifestations and the discovery of the genital lesion varied widely, but in the majority it was 5 years or more.

In Table II, patients with a previous history of pleurisy are separated from the other categories. In this connection, a difficulty arose which is encountered by most people who undertake an inquiry of this type, and

Table II. History of previous extragenital tuberculosis (177 cases)

Abdominal tuberculosis, usually proved at laparotomy	91
Pulmonary tuberculosis	29
Bone and joint tuberculosis	11
Renal tuberculosis	1
Tuberculosis of neck glands	1
Tuberculous abscess of groin	1
Pleurisy	79
Erythema nodosum	1

this is to decide how much significance should be attached to a previous history of pleurisy as distinct from pleurisy with effusion. True dry pleurisy is not infrequently due to the tubercle bacillus, but, unfortunately, "pleurisy" is one of the most abused terms in medicine and is often applied to conditions in which there is no inflammation of the pleura and in which the only feature in common with true pleurisy is pain in the chest. Pleural effusion was present in many patients in this group but by no means in all. In practically all the others, however, x-ray examination of the chest showed evidence of healed pulmonary tuberculosis. In the small number of cases without such history or x-ray evidence, it can only be assumed that the condition was probably tuberculous in nature. For similar reasons, the one patient with a history of erythema nodosum is included in the same category.

Age incidence. With reference to the age incidence, the average age was 28 years at the first attendance, the youngest patient being aged 16 years and the oldest 53.

Obstetrical history. Thirty-one patients were unmarried. Among the remaining 294, only 38 gave a history of previous pregnancy. The details of these pregnancies are shown in Table III.

This low incidence of fertility in cases of female genital tuberculosis is now widely recognized, and a considerable volume of liter-

ature has accumulated on this subject. In a previous paper, attention was drawn to the fact that the development, or at least the discovery, of a chronic form of endometrial tuberculosis in the postpartum period is by no means uncommon.⁵ In the present series there are no less than 9 cases (2.8 per cent) in which the tuberculous lesion probably developed during pregnancy or in the postpartum period. These patients usually complained either of bleeding or of abdominal pain dating from childbirth or miscarriage. Diagnostic curettage revealed endometrial tuberculosis in each case, and this condition should be kept in mind when patients with similar histories are being investigated.

Table IV. Principal symptoms (325 cases)

Infertility	142
Abdominal pain	76
Profuse and sometimes irregular bleeding	48
Amenorrhea, usually secondary	26
Vaginal discharge	19
No complaint	14

Principal symptoms. The principal symptoms are shown in Table IV. It will not be possible to discuss the symptomatology of these cases in any detail, and attention will be confined to the principal complaint in each case. Infertility was the most common symptom, and this finding is in keeping with most recent work on this subject. Pain was also a common symptom, varying in character and degree and situated in the lower abdomen. The next complaint in order of frequency was abnormal uterine bleeding, usually rhythmic but sometimes irregular and occurring several times in patients under 20 years of age. Of the 26 cases of amenorrhea, only 2 were of primary type and the remainder were secondary.

Nineteen patients complained only of vaginal discharge, and the existence of unsuspected genital tuberculosis was revealed by curettage. In most of these cases, however, there was either cervical or vaginal infection sufficient to explain the discharge, which cleared up after treatment of the local con-

Table III. Obstetrical history (38 patients)

<i>Previous pregnancies</i>	<i>Number of patients</i>
1 full-term pregnancy	13*
2 full-term pregnancies	6
1 abortion	5
3 full-term pregnancies	4
2 abortions	3
1 tubal pregnancy	2
9 full-term pregnancies	1
4 full-term pregnancies	1
3 full-term pregnancies and 1 abortion	1
2 full-term pregnancies and 1 abortion	1
3 abortions	1

*Includes one twin pregnancy.

dition. It seems probable that vaginal discharge is not a characteristic symptom of genital tuberculosis. Fourteen patients made no complaint of any kind when they were referred but invariably gave a history of some previous tuberculous infection, usually abdominal and detected at laparotomy.

General examination. A thorough general examination was carried out in all cases. Apart from a few of the earlier cases, each patient was seen by a chest physician and the chest and abdomen were x-rayed. X-ray examination of the chest revealed 8 active pulmonary lesions and 143 healed pulmonary lesions, and one of the latter group was associated with a positive sputum. X-ray examination of the abdomen showed calcified glands in 43 instances. A catheter specimen of urine was taken for guinea pig inoculation in almost every case, and the result was positive in 6 instances, a few of the most recent results not yet having been received. An interesting point in connection with these results is that they revealed evidence of hitherto unsuspected extragenital tuberculous lesions in no less than 77 patients with no history of such conditions. If the two methods of investigation are combined, namely, the history of previous extragenital tuberculous lesions on the one hand and radiological or bacteriological evidence of them on the other, 254 (84.3 per cent) of the 325 patients were found to have had at least one previous extragenital tuberculous lesion.

Pelvic examination. In the present series of 325 cases of genital tuberculosis, the endometrium was involved in 318, the Fallopian tubes only in 5, and the cervix only in 2. As has been mentioned previously, it is

almost certain that the tubes are affected in most if not all of the cases of endometrial tuberculosis. The findings on pelvic examination are seen in Table V. Since a number of patients had multiple lesions, the total number exceeds 325. It has been my practice to carry out cervical biopsy in patients with suspected or proved genital tuberculosis and cervical erosion and, in the present series, unsuspected cervical tuberculosis was discovered on 6 occasions in this way, including two cases in which the tuberculous infection was ultimately found only in the cervix.

Tubal patency. Out of 142 patients complaining primarily of infertility, tubal insufflation or hysterosalpingography was performed in 112, and the tubes were found to be blocked in 71 of these (63.4 per cent).

Diagnosis

As far as the cases of endometrial tuberculosis are concerned, a diagnosis was based initially on the histological findings in the curettings in most cases, although in a few the histological appearances were inconclusive or negative and bacteriological confirmation was awaited. These latter cases were previously diagnosed as endometrial tuberculosis in other hospitals. Diagnosis of tuberculosis of the cervix was also based initially on the histological appearance, and bacteriological confirmation was sought in each case. In the 5 cases in which the tuberculous infection was apparently limited to the Fallopian tubes, a diagnosis was made on histological examination of tissue removed at laparotomy. Vaginal swabs were taken in most of the earlier cases in an attempt to identify the tubercle bacillus. Out of 231 cases of proved endometrial tuberculosis, positive results were obtained in only 18. It is thus apparent that the routine taking of vaginal swabs for diagnostic purposes is not justifiable in cases of suspected female genital tuberculosis.

Bacteriological findings

Bacteriological proof of the tuberculous nature of the lesion was sought in 286 of

Table V. Findings on pelvic examination (325 cases)

Adnexal swelling, usually bilateral	156
Erosion of cervix	44
Retroversion of uterus	36
Cystic enlargement of one ovary	7
Uterine fibroids	4
Pyometra	1
No palpable abnormality	111

the cases, and a positive result has so far been obtained in 198. The routine adopted in the examination of specimens was that each specimen of endometrium or cervical tissue was divided into two approximately equal parts, one of which was prepared for histological examination and the other for injection into guinea pigs and inoculation of culture media. It is likely that the very small amount of tissue obtained by curettage in many instances may be the main reason for the rather high number of negative results.

Type of organism. In almost all cases with positive bacteriological findings, an attempt was made to type the organism. This has so far been successful in 147 instances, the tubercle bacilli invariably being of the human type.

Table VI. Sensitivity of organisms to various drugs

<i>Sensitivity</i>	<i>No.</i>
Streptomycin sensitive	145
Streptomycin resistant	8
Isoniazid sensitive	56
Isoniazid resistant	15
PAS sensitive	33
PAS resistant	1

Drug resistance. The resistance of the organism to various drugs was tested and the results are shown in Table VI. Sensitivity to streptomycin was tested in all possible cases, and testing of sensitivity to isoniazid and PAS was a routine procedure in the later cases. A number of sensitivity results are still awaited in the most recent cases in the series.

Management

Control cases. Thirty-eight of the earlier cases of endometrial involvement were initially allocated to a control group, as they formed part of an investigation into the efficacy of streptomycin and PAS in the treatment of endometrial tuberculosis. When this investigation was being planned, it was decided that the best way to ascertain the value of the drugs concerned would be in the form of a controlled trial. At that time, pre-

vious experience did not suggest that to withhold treatment was likely to involve any appreciable risk to the patient in most cases, but it is now apparent that this view was not correct.^{7, 9, 10}

It was accordingly decided to include control cases, under the following conditions: (1) all control patients whose disease was still active at the end of an observation period of one year should receive a full course of treatment; (2) all control patients showing any clinical deterioration should be withdrawn from the trial and treated at once; (3) all cases in which it was felt that it might be harmful to withhold treatment should be excluded from the trial and treated at once; (4) no patients with active extragenital tuberculous lesions should be included in the trial.

During the year of observation in this group, no active treatment of any kind was carried out. These patients were kept under observation and reported regularly, endometrial biopsy being carried out at intervals of 3 months when possible. The results in the control group of cases are shown in Table VII. It will be seen from this Table that 30 patients (78.9 per cent) were found to be either positive at the end of the control year or later or required treatment before the end of the control year because of clinical deterioration. Five patients defaulted during the control year and in only 3 was the endometrium consistently negative at the end of the control year and subsequently. It is thus apparent that the vast majority of patients with endometrial tuberculosis who do not receive drug treatment do not undergo spontaneous cure.

Table VII. Results in control group (38 cases)

<i>Results</i>	<i>No.</i>	<i>%</i>
Positive at end of year	21	55
Required treatment during year	7	18
Negative at end of year but later positive	2	5
Defaulted during year	5	13
Negative at end of year and subsequently	3	8

The patients in whom the condition persisted or recurred will be considered further in a later section. There were 7 patients who required treatment during the control year, 5 with flare-up of the tuberculous condition in the pelvis, one with tuberculous meningitis, and one with a reactivation of a healed pulmonary lesion. Of the 2 patients whose endometrium was negative after one year but later became positive, in one the condition recurred for the first time after 4 years' observation. The 3 patients whose endometrium has remained negative throughout may be examples of spontaneous healing or of cure following curettage, and this question will be considered further in a later section.

Treatment of cases without bacteriological proof. Some doubt has been expressed as to the advisability of treating patients with tuberculosis of the endometrium unless bacteriological proof has been obtained. My view is that such patients should be treated on the basis of the histological findings only and it is my regular practice to do so, without awaiting the bacteriological results.⁸ There were 128 patients (39 per cent) in whom the tubercle bacillus has not so far been found, although in 35 of these bacteriological proof was not sought initially for various reasons. In 80 of these 128 patients either there was a previous history of an extragenital tuberculous lesion, or evidence of such a lesion was discovered by x-ray examination of the chest or abdomen.

The histological appearances in those cases lacking bacteriological proof are identical with those in the remainder, and there is no doubt that they are true examples of endometrial tuberculosis. As mentioned before, it seems probable that the quantity of endometrium obtained plays an important part in this matter. It is a constant finding that in histologically positive cases in which ample endometrium is obtained for guinea pig inoculation and culture, the results are almost invariably positive. On the other hand, where the amount of tissue is small, there is an appreciable risk of getting a negative bacteriological result although the his-

tological findings are positive. Another aspect of this problem is the fact that the disease in the endometrium is essentially focal in character in the vast majority of cases. In some specimens of endometrium, the lesions are very scanty and it may well be that no tubercles are present in the tissue used for guinea pig inoculation or culture.

Drug treatment. Various schedules of drug treatment were employed, depending on circumstances. Treatment was almost always given on an outpatient basis except for a small group of patients who had a pelvic spread of the disease following the initial curettage. These patients with acute symptoms were admitted to the hospital as emergencies and the earlier part of the drug schedule was administered there. It was usually possible to discharge them after 2 or 3 weeks, the remaining treatment being given to them as outpatients. Most of the patients received treatment either at the outpatient department of the David Elder Infirmary or from their own doctors. They were ambulant throughout and many continued to work. In no instance was it considered necessary to admit these patients to sanatoriums, except in a few cases of extragenital spread of the tuberculous process.

Drug treatment was employed in 293 of the 325 patients. The remaining 32, who did not receive treatment of any kind, will be considered later. The treated patients can be divided into 4 main categories.

1. Streptomycin and PAS. The first group were treated with streptomycin and PAS. The course given in the earlier cases in this category was 1 Gm. of the calcium chloride complex of streptomycin daily for 84 consecutive days, with 3 Gm. of the sodium salt of PAS four times daily over the same pe-

Table VIII. Results of treatment with streptomycin and PAS in 165 endometrial cases

Results	No.	%
Remained negative after treatment	111	67
Recurred after treatment	35	21
No follow-up	19	12

riod. In the later cases, streptomycin sulfate was substituted for the calcium chloride complex and the daily dosage of PAS was increased to 20 Gm. Including 25 control patients requiring treatment, 168 patients were treated with streptomycin and PAS, the last 78 being on the second schedule. Included in this group was one patient with tuberculosis apparently limited to the cervix and 2 cases in which only the Fallopian tubes appeared to be involved.

An attempt has been made to keep all treated patients under observation indefinitely, although in many instances this has not proved feasible. During the first year following the commencement of treatment, in the patients with endometrial infection, the condition has been observed by endometrial biopsy, usually carried out every 3 months in the premenstrual phase of the menstrual cycle. This procedure was almost always performed at the outpatient department, and general anesthesia was used only in the occasional patient who was admitted to the hospital for one or two days for this purpose.

At the end of the first year of follow-up, admission for full curettage under general anesthesia was arranged, and subsequent control was conducted mainly by endometrial biopsy at intervals of 6 to 12 months. A good deal has been said and written about the risks of endometrial biopsy and of dilatation and curettage in patients with genital tuberculosis. My experience is that full curettage is definitely risky in the untreated patient and that an occasional pelvic flare-up inevitably occurs following the initial curettage in patients in whom genital tuberculosis is unsuspected. Even in treated cases, it is probably unwise to carry out full curettage unless there have been at least two consecutive negative endometrial biopsies previously.

Endometrial biopsy is certainly less risky than full curettage, and no trouble has occurred after its use in treated cases, provided that it is carried out gently and carefully by an experienced person. Despite every care, however, endometrial biopsy was occasionally followed by pelvic flare-up in the con-

trol cases, and further work with controls does not now seem justified. The only reason for using full curettage in suspected cases of genital tuberculosis is that it yields a larger amount of tissue than endometrial biopsy and thus the chance of discovering tubercle bacilli, if present, is increased.

These remarks, of course, do not apply to the 3 cases in this treatment group in which endometrial involvement was not proved, although even in such cases an endometrial examination is carried out at least once each year in the follow-up period if possible. The patient with only cervical involvement had cervical biopsy and dilatation and curettage 14 months after treatment, with negative result. Two years later, she was readmitted with a ruptured tubal pregnancy; the tube which was removed showed evidence of chronic inflammation but not of tuberculosis. She has not since reported. The 2 patients with tuberculosis apparently limited to the Fallopian tubes have been seen at regular intervals, progress being checked by pelvic examination and by occasional endometrial biopsy. They have remained well and there has been no recurrence of pain or of adnexal thickening and tenderness.

The results in the 165 cases of endometrial infection are shown in Table VIII. It will be seen from this Table that 111 patients (67 per cent), had a persistently negative endometrium following treatment, the average duration of the follow-up being 31 months. One of these patients later developed a reactivation of a previously healed pulmonary lesion and required a further course of drugs. In addition to the follow-up of the pelvic condition, the question of further extragenital infection is always kept in mind and repeat x-ray studies of the chest and examination of the urine are carried out from time to time, as indicated in the individual case.

Thirty-five patients (21 per cent) had recurrence of the endometrial infection, and most of these received additional treatment of one kind or another. The average time after treatment at which recurrence was diagnosed was 25 months, and these cases will be considered further in a later section.

Table IX. Results of treatment with streptomycin and isoniazid in 70 endometrial cases

Results	No.	%
Remained negative after treatment	59	84
Recurred after treatment	9	13
No follow-up	2	3

The remaining 19 patients (12 per cent) had no follow-up, some not having completed treatment and others defaulting at the end of treatment.

2. *Streptomycin and isoniazid.* The second group of patients were treated with streptomycin and isoniazid. This combination of drugs was used in 71 further patients, 5 of whom were previously controls. In 70 of these cases, tuberculous infection of the endometrium was present. In the remaining patient, the infection was apparently limited to the Fallopian tubes, and she has since remained clinically well at follow-up.

The dosage employed was 1 Gm. of streptomycin sulfate daily for 84 consecutive days combined with 100 mg. of isoniazid twice daily over the same period. The results are shown in Table IX. It will be seen that 59 cases (84 per cent) have so far remained negative after treatment, the average duration of follow-up being 29 months. It is not possible from these figures to say that the results obtained with streptomycin and isoniazid are better than those obtained with streptomycin and PAS, as the latter group were followed for a rather longer average time, and a number of the recurrences were in the second and third years after treatment. This matter has been considered in some detail in a recent publication.¹¹

3. *PAS and isoniazid.* The third group of patients were treated with PAS and isoniazid. There were 52 patients in this category and all but 2 of them received either a 6 or a 12 month course. These 2 patients were treated with a 3 month course of the drug combination, and the endometrial infection has since recurred in each and has necessitated further drug treatment. The remaining 50 patients, including all the more recent

ones, have received either a 6 or a 12 month course. The daily dosage employed was 12 Gm. of PAS and 200 mg. of isoniazid, the drugs being administered together in the form of cachets.

In 2 of these 50 cases the infection was apparently limited to the Fallopian tubes. One of these patients has since remained clinically well at follow-up and the other has not reported. The results obtained so far in the 48 cases of endometrial involvement are encouraging, but it is too early to compare them with those in the other categories. All of the 29 patients so far followed for an average period of 16 months, have remained negative. One further patient, who has not so far had an endometrial examination since starting treatment, had what appeared clinically to be a pelvic flare-up and was given an additional 3 month course of streptomycin with complete relief of symptoms. It is hoped that these longer periods of treatment will ultimately yield better results than those achieved with the shorter courses.

4. *Isoniazid alone.* The remaining 2 patients were treated with isoniazid alone. One was admitted to a sanatorium following a pelvic flare-up and could not be traced after dismissal. The other patient had already had

Table X. Results in 55 patients with histological or clinical recurrence after first course of treatment

Results	No.
Cured after second course	20
Surgical intervention after first course	8
Surgical intervention after second course	5
Second course refused	5
Surgical intervention after third course	4
Positive after second course, negative after third course	4
Second course in progress	3
Surgical intervention after fourth course	1
Positive after second course, third course in progress	1
Defaulted after second course	1
Positive after third course, fourth course in progress	1
Positive after third course, negative after fourth course	1
Positive after second course, defaulted after third course	1

full treatment with streptomycin and PAS in another hospital and was given isoniazid, 50 mg. twice daily, for 84 consecutive days. Her endometrium has remained negative for 20 months following this treatment. Although this patient (and several others about to be mentioned) received isoniazid alone, it is now generally agreed that the use of a single drug is undesirable, and this method has consequently been abandoned.

Recurrence of infection. There were 46 patients showing histological recurrence of the endometrial infection following initial treatment with one or other of the drug combinations, and 9 others developed clinical evidence of recurrence of tuberculous infection in the pelvis. These 9 patients had either abdominal pain, accompanied by adnexal thickening and tenderness, or a marked increase in the size of the adnexal masses. In cases of this type with probable pelvic flare-up, additional drug treatment was instituted without endometrial examination, and further curettage or endometrial biopsy was withheld for at least a year.

Various additional lines of treatment were adopted in these cases. The earlier patients received isoniazid, in doses of 50 mg., and later 100 mg., twice daily for 84 days. Some time ago, the use of isoniazid alone was abandoned, and two drugs in combination were employed instead. The exact drug combination used varied with the individual case and with the sensitivity of the organism, but, recently, PAS and isoniazid have usually been employed. The results are shown in Table X, and it will be seen that a substantial number of patients remained negative after a second course of treatment. Eighteen patients have so far been treated by operation and this group will be considered later in some detail.

Toxic drug reactions. Toxic drug reactions occurred in a disturbingly large number of patients, and treatment had to be stopped before the end of the course in no less than 39 of the 293 patients treated with drugs (13 per cent). Streptomycin was the drug responsible in 26 of these, vestibular disturbance occurring 22 times and skin rashes 4

times. In one of the latter cases, the generalized skin eruption was very severe, and there was loss of most of the hair from the patient's scalp. The total dosage of streptomycin administered before the onset of the toxic symptoms varied between 11 and 63 Gm. The 13 remaining toxic reactions were due to PAS, each patient having a severe generalized upset, although the symptoms varied with the individual. All the patients in this group had some gastrointestinal disturbance and 2 had a skin eruption. The total dosage of PAS before the onset of these symptoms varied between 147 and 1,300 Gm. One of these patients also showed sensitivity to isoniazid.

Although treatment had to be discontinued in all 39 patients, no permanent ill effects of any kind were observed. Even the patient who lost most of her hair improved rapidly after cessation of treatment and her hair has now returned to normal. In the more recent cases, a change was made from the calcium chloride complex of streptomycin to streptomycin sulfate in the hope that this would reduce the incidence of toxic manifestations. Unfortunately, this has not proved to be the case, although painful injections are much less frequent with the latter preparation. In addition to the cases just described, minor upsets occurred in an appreciable number but in these the full course was completed, sometimes after a stay in the hospital for desensitization.

Cases treated surgically. Eighteen patients in the present series have so far been treated surgically. In 16 of these cases, the operation was performed by myself and the remaining 2 were done in other hospitals in Glasgow.

At present, the indications for operation are as follows:

1. Persistent or recurrent abdominal pain associated with adnexal masses after at least one full course of drug treatment.
2. Recurrence of endometrial infection after at least one full course of drug treatment.
3. The persistence or development of large adnexal masses after at least one full course of drug treatment. In this connection,

the possibility that the masses may not be tuberculous in origin must be kept in mind.

Of the 18 operations in the present series, 14 were performed because of pain, 3 because of endometrial recurrence, and one because of a persistent adnexal mass which was found at operation to be a very large tuberculous pyosalpinx. My impression at present is that the indications for operation will tend to become wider, rather than narrower, in the future. A preoperative course of all 3 antituberculous drugs was started at least 2 weeks before operation in each case, unless a previous drug reaction had occurred, in which case only the other 2 drugs were given. The length of this course varied with the individual case but the streptomycin was usually given for 3 months and the PAS and isoniazid for at least 6 months.

As the operation is performed to cure the tuberculous pelvic condition, it is considered that radical surgery is indicated. My practice is to perform total hysterectomy and removal of both tubes and ovaries by the abdominal route, irrespective of the age of the patient. This was done in all 18 cases except one treated in another hospital, when part of one ovary was left. In all my personal cases, the ovaries have been most unhealthy and densely adherent to the Fallopian tubes and other surrounding structures, and it was felt that conservation of such ovaries would not be in the interest of the patients.

At laparotomy, although adhesions have invariably been widespread, a striking feature is the relative ease with which it has been possible to perform these operations. This has been in marked contrast to the extreme difficulty encountered in the past, and it is likely that this is due to the preoperative administration of antituberculous drugs. An interesting feature was the invariable finding at operation of a very high bladder, sometimes coming to within less than an inch of the fundus of the uterus. All patients treated surgically have progressed satisfactorily except one with disruption of the abdominal wound, which required re-suture. No patient developed a fistula and

this complication, which used to be relatively common, should rarely occur today. At follow-up, menopausal symptoms were usually troublesome but responded well to estrogen therapy.

In relation to surgical treatment, each case should be carefully studied as an individual problem before deciding on operation. The indications previously mentioned are only for general guidance, and a number of other factors should be taken into account, including age, parity, primary complaint, previous drug treatment, drug reactions, sensitivity of organism, pelvic findings, tubal patency, previous health, and the presence of active extragenital tuberculous lesions.

Cases in which no treatment has been employed so far. There were 32 cases in the present series in which no treatment has so far been employed. One of these patients was found to have tuberculosis apparently limited to the cervix in another hospital and was then referred to my department. An extensive cervical biopsy was carried out with negative result, and this patient has since attended on several occasions. At each visit, the cervix has appeared to be perfectly healthy on speculum examination, and it has not been thought so far that drug treatment was necessary in this case.

Six patients with endometrial involvement, including 5 from the control group, did not attend after the initial examination. The remaining 25 patients in this category all had endometrial infection, 3 being control cases and 22 being referred from other hospitals after the initial diagnosis had been made. So far, no evidence of endometrial tuberculosis has been found in these patients and most of them still attend regularly. The average length of time between the initial diagnosis and the last examination of the endometrium in this group is 30 months.

It is hoped to keep these patients under observation indefinitely, and it is quite possible that recurrence of the endometrial infection may ultimately show up in some of them. At present, they can presumably be regarded as examples of spontaneous healing or of cure following curettage. One of the

patients in this group, who complained of infertility and had patent Fallopian tubes, later had a normal full-term pregnancy. Another patient, complaining initially of lower abdominal pain, was free of symptoms when she was referred to me and has since had 2 abortions.

Symptomatic results

In relation to the symptomatic results, it is worthy of note that no significant differences have been observed in the different treatment groups. The most common presenting symptom was infertility, which was present in 142 cases. Thirteen patients have so far become pregnant, most of these complaining primarily of infertility. Five patients had ruptured tubal pregnancies, one had 2 successive ruptured tubal pregnancies, and one had a ruptured tubal pregnancy followed by a full-term pregnancy, with delivery of a healthy child. Two patients had abortions, one before drug treatment was started, the other during drug treatment. A further patient, who did not receive treatment of any kind, has had 2 abortions since first attending.

One patient is pregnant at present and 2 others have each had a normal delivery of a healthy child, one of the latter not having received any treatment. While these results are disappointing, they are not at all surprising. Examples of pregnancy occurring in patients with a history of proved genital tuberculosis are infrequent in the literature, although a number of cases have been reported recently. It is likely that the low fertility of these patients is related to the high incidence of blockage or morbidity of the Fallopian tubes. While drug treatment may arrest the active infection, the disorganization of tubal structure, which has already occurred, may be such as to make restoration of normal function impossible.

The results of treatment in relation to the remaining complaints were generally satisfactory. Of 71 treated patients complaining of abdominal pain, 60 reported after completion of the course. Fifty-one were completely free of pain, 4 were considerably improved

and only 5 reported no improvement. There were a number of patients with recurrence of pain, however, and most of these patients with persistent or recurrent pain received further drug treatment. So far, it has been necessary to employ surgery in 14 patients in this group. The effect of drug treatment on the adnexal masses was varied. In many cases, the swellings were no longer palpable after treatment, and, in many cases, they were considerably reduced in size. In a few patients, however, especially in those with persistent pain, there was no apparent change in these masses.

Forty-five treated patients complained of profuse and sometimes irregular bleeding. Thirty-five of this group attended after treatment and all reported a return to a normal menstrual cycle. The results in the cases of amenorrhea were also satisfactory. Of 25 treated patients with amenorrhea, 18 returned after completion of the course. Twelve reported restoration of normal menstruation, including one patient aged 24 with primary amenorrhea. No change was reported by the 6 remaining patients, 2 of whom were over 40 years of age. The 5 treated patients with cervical tuberculosis all had complete healing of the cervical lesion, as shown by cervical biopsy and by examination with a speculum.

Summary

A study has been made of 325 cases of genital tuberculosis in women. A history of previous extragenital tuberculosis was obtained in 177 of these, and 77 further patients showed radiological or bacteriological evidence of such conditions. Of 294 married patients, only 38 gave a history of previous pregnancy.

The principal complaints were infertility in 142 cases, abdominal pain in 76 cases, uterine bleeding in 48 cases, amenorrhea in 26 cases, and vaginal discharge in 19 cases. Of the 325 cases in the series, the endometrium was involved in 318, the Fallopian tubes only in 5, and the cervix only in 2.

Diagnosis was based initially on the histological findings, but bacteriological con-

firmation was usually sought and has so far been obtained in 198 cases. The organism has so far been typed in 147 cases, all of these being of the human type.

Thirty-eight control patients with endometrial infection were observed for one year without treatment. In 79 per cent the infection persisted or recurred or treatment was required during the control year because of clinical deterioration.

One hundred sixty-five patients with endometrial tuberculosis were treated with streptomycin and PAS, and 67 per cent remained negative after an average follow-up period of 31 months. An additional 70 patients with endometrial involvement were

treated with streptomycin and isoniazid, and 84 per cent remained negative after an average follow-up period of 25 months. PAS and isoniazid were used in 50 other patients with involvement of the endometrium. Of 29 who were followed for an average period of 16 months, all have so far remained negative. Toxic drug reactions sufficient to necessitate cessation of treatment before the end of the course developed in 39 cases (13 per cent).

Surgery was employed in 18 patients, all of whom had at least one course of drug therapy previously. Apart from patients complaining primarily of infertility, the symptomatic results after drug treatment were generally satisfactory.

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A study of patients admitted to a psychiatric hospital after pelvic operations

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THIS study is based on female patients admitted to the Syracuse Psychiatric Hospital during the year 1958 whose illness seemed to be related to pelvic operations. Attention was drawn to this group because it was almost twice as large as the number of women admitted following operations of of *all* other types.

The data which forms the basis for this report were gathered from psychiatric investigations made during the hospital stay. Information also was gathered from one or more relatives who were interrogated by a social service worker. In addition, I interviewed 8 of the 9 patients. These interviews were tape recorded and the quotations which will be presented are largely derived from this source. In all but one instance, surgical and pathological reports were also obtained.

The clinical data will be analyzed both statistically and psychodynamically.

Incidence

During the year 1958, 203 women were admitted to the Syracuse Psychiatric Hospital, an institution serving primarily as an acute treatment center for Syracuse and the surrounding area. Of this number, there were 9 patients ($4\frac{1}{2}$ per cent) in whom pelvic operation was seemingly a precipitating factor for the psychiatric disorder. Although the sample is small, the figure would seem to be in keeping with general clinical

experience. It stands in sharp contrast to the number of female patients admitted following operations of all other kinds. This number was 5 ($2\frac{1}{2}$ per cent).

It is interesting, too, to compare these figures with the number of patients whose admissions were related to childbearing. There were 19 in this group ($9\frac{1}{2}$ per cent). Of the 19 patients, 15 were admitted post partum, 3 ante partum and one both ante and post partum. The percentage would be much higher, of course, if it were based only on patients in the childbearing years.

Twenty-one of the total number of women admitted had had pelvic operations in the past without reactions resulting in psychiatric hospitalization. In other words, the present illness occurred many years after the surgical experience and seemed unrelated to it.

This study

All 9 patients in this study were (or had been) married. Seven had children. The largest number of children was 4 (two women). In every instance the growth for which the operation was performed was benign. Most of the admissions to a psychiatric hospital occurred between 2 weeks and 5 months postoperatively. In one instance, however, the patient was not hospitalized until 16 months postoperatively. The symptoms which ultimately led to this result had begun within a week of the operation. In another instance, a hysterectomy had been performed 5 years previously. This patient, however, had been home for only 2 months

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since her first hospitalization 5 weeks post-operatively.

Seven of the 9 patients were premenopausal. Of these, 5 had had both ovaries removed. The nature of the reactions responsible for psychiatric hospitalization were: depression, 7, and schizophrenia, 2. Significantly, all of the depressed patients were clinically agitated. This finding is in agreement with Lindemann's¹ observation. Five patients reported previous periods of depression, but none had been admitted to an institution before. Lindemann,¹ in his study, noted that a previous period of depression predisposed to this reaction following pelvic operation. One of the 2 schizophrenic patients had been treated as an office patient with electroshock therapy some years previously. It was impossible to obtain the diagnosis made at that time.

Case report

Before proceeding to a discussion of the dynamic factors which were identified in this series of patients, one brief case report will be presented as an illustration of the type of material which was gathered.

Two months prior to her admission to the Syracuse Psychiatric Hospital, Mrs. N. (age 38 and the mother of 4 children) had had an epidermal inclusion cyst of the vagina removed. On the ninth postoperative day she began to hemorrhage and a "suture ligation and a blood transfusion" were required. After returning home she became depressed and anxious and thought that people were staring at her.

Five years before, a panhysterectomy and a left salpingo-oophorectomy had been performed. The pathological diagnosis was adenomyosis uteri and hyperplasia of the endometrium. Approximately 2½ weeks postoperatively, she had become depressed and anxious. "I got nervous then like now. I felt like I wasn't a woman any more. I could not have any more children. (Tears.) I didn't think my husband loved me any more. I didn't feel attractive. I didn't feel that people liked me." She went on to explain that she regarded herself as sexually disfigured and that she was practically without sexual desire. "It was months after the hysterectomy before I had any sexual desire and then

it was never very often." She began to imbibe alcohol. "Maybe I did it because then I didn't think I was so ugly. After drinking I could have some sexual feelings." She would pick up men at the bars she frequented and would have sexual relations with them. Following these encounters she would inform her husband of what she had done. She became extremely upset when he simply stated that he loved her but did not become angry.

It is of interest to note that in the 5 years which had intervened between the hysterectomy and the operation on the vaginal cyst she had undergone 4 other surgical procedures. These involved varicose veins, hemorrhoids, an umbilical hernia, and a vaginal cyst. It was only after the second pelvic operation 3 years previously that she had become markedly depressed. When she mentioned this, she added: "I just feel like I am a freak."

For at least a month prior to her most recent operation, she had deferred consulting a physician, in spite of considerable pain, because she was afraid that a surgical procedure would be advised.

When it was suggested that the vaginal operation had rekindled her feelings about the hysterectomy, she responded: "There is not much left of me to be a woman. They keep cutting away." (She cried for several minutes.)

When asked if her reaction was related to feelings which she had had in the past, she stated: "I never felt pretty. I was always called homely by my sisters and brothers. For a long time I was called ugly. I would cry. It hurt." Actually, judged by our usual standards she was a plain but not an unattractive woman. After talking about the attitude of her siblings, she went on to speak of how her mother had always picked on her. Her mother had, also, been unwilling to believe that an older brother had forced himself on her sexually.

Comment. In this instance, the patient had had a lifelong struggle with the feeling that she was unattractive—especially as a woman. In view of this, psychologically she could ill afford an operation involving her female reproductive organs. From her viewpoint, this had altered her sexual capacity and attractiveness. She then felt as though she were even less of a woman than she had been previously. She struggled to counterbalance this picture of herself through the use of alcohol and sexual relations with many men. In addition, she reported her be-

havior to her husband. It might be assumed that she had hoped he would become angry which, among other things, would have proved that he regarded her as a desirable woman. His response, like her mother's, may have meant to her that he did not consider her attractive to men and, hence, did not believe her stories.

The vaginal operations served to rekindle all the feelings she had had following the hysterectomy, and besides that they were regarded as additional assaults on her femininity. Although she had had 4 children, she was upset by the removal of her ability to have more children. This ability—as well as the fact of having children—was important in combating the feeling that she was a “freak.”

Pelvic operation and sexual function

There was remarkable consistency in the belief that the removal of the uterus and ovaries meant the end of all sexual life, at least in a feeling way. To illustrate this point and to elucidate on it, I shall quote from the clinical data which were obtained.

One woman, who was postmenopausal at the time of operation, stated that she had taken it for granted that the hysterectomy would result in the cessation of her sexual feelings. She had not asked her physician whether or not this would be so. Significantly, she “had never cared much for sex.”

A second woman related that she did not think that she would be “sexually inclined” after her operation. She had not broached the subject with her gynecologist because she did not feel free to discuss it with anyone. She had requested, however, that part of one ovary be left. Her belief was that she would then remain “sexually inclined.”

A third woman assumed that the operation would affect her sexual life but she was unwilling to discuss the subject. She did state, however, that she had hoped that it would not have been necessary to remove her ovaries and tubes. When she was informed that these had been removed, she exclaimed, “Gee! I have a husband!”

A fourth woman felt that she would no longer be any good for her husband sexually. She cried during intercourse and complained of an inability to have feelings. She believed

that the operation had deprived her of sexual feelings and converted her into a “blank person.”

The question arises as to why women (and perhaps men, too) assume that a hysterectomy and salpingo-oophorectomy spell the end of sexuality in a feeling way. It should be noted that the idea may persist in spite of physicians' statements to the contrary. This misconception may be the result of a theory concerning sexuality which is based on anatomy and physiology to the exclusion of psychology—or, to state it another way, on the body to the exclusion of the mind. (It, of course, also excludes the vagina and clitoris.) Moreover, it is modeled on the anatomy and physiology of the male sexual function. Thus, the removal of the uterus and ovaries is pictured as having an effect similar to the removal of the penis and testicles.

It might be added parenthetically that the wish, however ambivalent, for the end of conflict-producing sexual feelings may be a contributory factor.

In connection with the notions which have been mentioned concerning the effects of pelvic operations on sexual feelings, the findings of Drellich and Bieber² are pertinent. They stated: “The concept of the uterus as being in some way important in maintaining sexual functioning was verbalized by 15 [of 23] women. Preoperatively some feared that the hysterectomy would cause a lessening of their sexual desire and a decrease or disappearance of their ability to respond sexually. Some feared that there would be a loss of sexual attractiveness with resultant loss of their husbands' interest. . . .”

Pelvic operations and childbearing function

The loss of the ability to bear children may produce profound psychological reactions. This is true whether or not children are consciously desired. The ability to have children, even if it is never used, is of significance in the self-image of a woman. It is the loss of this ability that gives rise, in part, to such statements as, “I am a neuter,”

"I am a blank," and "I am no longer a woman." One patient, who had been unwilling even to adopt children, spoke of herself during her postoperative schizophrenic reaction as feeble-minded. It seemed apparent that she displaced her feelings of being inadequate physically to being subnormal mentally. She also referred to herself as a "blank person" and complained that she felt "less like a woman." She followed this by speaking of her "blank mind" and of being feeble-minded.

The patient whose history was previously quoted in some detail stated that she felt that she was no longer a woman because she could not have more children. It seems likely that the *ability* to have children rather than the *desire* to have them was the crucial factor in this instance.

Two statements in the literature relate directly to this issue. The first³ is: "As long as the possibility of motherhood remains even theoretically possible, the woman feels intact as a female of the species. Once this reproductive capacity is permanently negated, the woman feels useless and no longer a 'whole woman.'" The second² is: "For some women, even though they desired no more children, the knowledge that they were able to bear children gave them the feeling of being complete and feminine, and the loss of childbearing ability was viewed as rendering a woman something less than a complete female."

Comment

The most striking finding in this study was the fact that almost twice as many women were admitted to a psychiatric hospital following pelvic operations as following all other types of operations. This finding was in keeping with Lindemann's¹ study in which he noted that agitated depressions occurred twice as often following pelvic operations as upper abdominal operations.

How do we explain this incidence? Surgical complications were not a factor. In only one case was there a complication (hemorrhage 9 days following the excision

of an epidermal inclusion cyst of the vagina).

Preoperative reactions did not seem to vary from what might be encountered in any group of surgical patients. Two women deferred seeking medical help for a period of months after the onset of symptoms. A third woman was reported to be "very difficult and unstable" prior to the operation. It was necessary to persuade her to remain in the hospital to undergo the recommended surgical procedure. In the other 6 patients, no preoperative problems were reported.

The nature of the illness in terms of gravity or threat to life would not explain the postoperative reactions. As previously mentioned, not a single patient in this series had a malignant growth. In two instances the pelvic complaint (pain) had occurred in the context of marital difficulties and was probably not related to a pathological lesion. In two other instances, however, the need for surgical intervention was pressing (hemorrhage from large fibroids). It could be argued, of course, that, in the presence of carcinoma, the reaction to the removal of pelvic organs might be more favorable. The organ would be regarded as a threat to life rather than a valued part of the body. This might explain, in part, the finding of profound reactions to the operative removal of organs with benign disease as contrasted with those with malignant disease. It would not, however, explain the high incidence of profound reactions to pelvic operations as contrasted with all other types of operations.

In regard to the specific effect on childbearing, it should be noted that 2 of the women were postmenopausal. Only 2 of the other women were childless, and one of them previously had been informed that her Fallopian tubes were occluded and that she would not be able to conceive. The other childless woman was afraid to even consider adopting a baby in spite of her husband's urging. Thus, the reactions cannot be attributed to an interference with childbearing.

The clinical data suggest that the relatively high incidence of profound reactions to pelvic operations is due to the meaning of these organs in the maintenance of an

acceptable self-image. The removal of the uterus and adnexa is experienced as a profound assault on feelings of womanliness in so far as these feelings are determined by the notion of being a sexual person and by the ability to have children. The fact that a woman had not enjoyed sexuality and had never intended to have children does not negate this thesis. The symbolic meaning in terms of completeness as a woman is the crucial factor. As Drellich and Bieber² stated: "Patients who had heretofore never consciously formulated their attitudes towards a particular organ of their body became aware that they harbored within themselves certain definite beliefs about their anatomy, their physiology, and the value of a particular organ in their total life adjustment."

It might further be assumed that those women who had been least secure in their concept of their own femininity would be most vulnerable to an operation on the genital organs. This would not mean, however, that they would necessarily have reactions which would require hospitalization. Many might respond with mechanisms of defense which would protect them from incapacitating symptoms.

It is my impression that the variables are so numerous that it is difficult, if not impossible, to predict the outcome of the defensive effort. Lindemann's¹ study, in which predictions were made preoperatively, bears this out. Only one factor was of predictive significance. He stated: "The most definite indication for the possible appearance of postoperative depressive symptoms is, from our series, the history of a previous depression. . . ."

The complexity of the situation is highlighted in the following case note: The patient had been depressed, agitated, and concerned about facial grimaces dating back to the week after a hysterectomy. These symptoms almost completely subsided for a period of a few weeks when she was entrusted with the care of her grandson. As she stated, this made her feel useful. The experience served to combat the feelings which had been mobilized by her operation

—feelings that her body was "not natural" and that she had been "made into another person." In speaking of her operation she made a slip of the tongue and referred to it as an accident. When her daughter-in-law gave up her job and took over the care of her son again, the patient's symptoms returned and with such severity that hospitalization was recommended.

In this instance a fortuitous occurrence had served to combat feelings of uselessness and probably those of being an incomplete woman. The termination of this arrangement after a few weeks, however, produced a profound letdown and a marked recrudescence of symptoms. It is possible that if there had not been this fortuitous occurrence, she might have gradually re-established her feelings of womanliness without requiring hospitalization. Or, if her grandson had remained with her longer, she might have maintained her favorable response to his presence.

In other patients in this series, various mechanisms of defense had been employed, but, for one reason or another, these had not adequately protected against a profound depression. For example, the woman whose case report was presented previously attempted to re-establish her feelings of femininity through the effects of alcohol and the medium of promiscuity. These efforts apparently helped but were not sufficient to ward off a depression following the third pelvic operation. She then became preoccupied with the feeling that she was disfigured and a "freak." This woman presented a lifelong story of struggling against a picture of herself as ugly which she attributed to her mother's and her siblings' attitudes toward her.

It can be postulated that the less secure a woman is in the early feelings concerning her femininity and attractiveness, the more intense will be the need for defensive measures to cope with the threat to the self-image imposed by the symbolic meaning of the removal of pelvic (sexual) organs.

Although self-image and defensive efforts are basic, other factors undoubtedly have

a contributory influence in determining the reactions to gynecological operations. These include the preparation of the patient for the operation, the attitude of the surgeon and other hospital personnel, and the current life situation of the patient, especially in terms of her relationship with her husband and children.

Summary

Of 203 women admitted to the Syracuse Psychiatric Hospital in 1958, there were 9 in whom a pelvic operation was seemingly a precipitating factor for the psychiatric disorder. This was in sharp contrast to the number of women admitted following operations of all other kinds (5 patients).

In 8 of the 9 cases, admission to a psychiatric hospital occurred between 2 weeks and 5 months postoperatively. The most common clinical picture was that of an agitated depression (7 patients).

There was a remarkable consistency in the belief that the removal of the uterus and ovaries meant the end of all sexual life, at least in a feeling way. It was as though the loss of these organs was pictured as hav-

ing an effect similar to that of the removal of the penis and testicles.

The loss of the ability to bear children may produce profound psychological reactions whether or not children are consciously desired. The ability to have children, even if it is never used, is of significance in the self-image of a woman.

The removal of the uterus and adnexa, because of their meanings in terms of sexual and childbearing functions, may profoundly affect the feelings of womanliness which are so crucial to the self-image. This would most likely lead to profound psychiatric disorders in those patients who have been least secure in this respect, and who, for one reason or another, are unable to mobilize adequate defenses. These factors would seem to account for the high incidence of adverse reactions to pelvic operations.

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OBSTETRICS

The ratio of male to female embryos as determined by the sex chromatin

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THE accepted secondary sex ratio of man the world over is approximately 106 males to 100 females. This figure has been arrived at by the examination of term and premature infants. Many attempts have been made to establish a sex ratio for fetuses of a younger gestational age. In general, such studies have been misleading for, as Wilson¹ has shown, external genitals are an unreliable index of sex before the 50 mm. stage. However, Tietze's tabulation,² which is based on the examination by Streeter of fetuses ranging from the third to the seventh month of gestation, stands as a classic. In that study the assignment of sex was based not only on gross inspection but also upon histologic examination of gonadal tissue. The male to female ratio in Tietze's series of 5,787 fetuses was 107.9:100 (Table I).

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This is similar to the secondary sex ratio of 106:100.

Since, theoretically, there should be as many Y-bearing as X-bearing sperm, the primary sex ratio, that is, the ratio that obtains at the time of fertilization, should be 1 to 1. If this is so and the secondary sex ratio is 106 to 100, male to female, then one might suspect that more females than males are lost during the early months of pregnancy. This, however, has remained speculative until the present time for there has been no known way of establishing the sex

Table I. Sex ratios of specimens in the Carnegie collection (Tietze)

Crown to rump length (mm.)	Month of gestation	No. of males	No. of females	Sex ratio
20-49	Third	58	62	93.5:100
50-99	Fourth	598	555	107.7:100
100-149	Fifth	771	667	115.6:100
150-199	Sixth	801	730	109.7:100
200-249	Seventh	775	770	100.6:100
20-249	Third to seventh	3,003	2,784	107.9:100

of a pregnancy in the absence of a fetus or embryo or in the presence of undifferentiated gonadal tissue. Barr's discovery³ of a morphological difference between male and female on the basis of the sex chromatin content of resting nuclei has paved the way for further insight into the problem. Particularly pertinent has been an extension of Barr's work by Graham,⁴ who showed by determination of gender by the sex chromatin that a morphologic sex difference was present in cat embryos before gonadal differentiation occurred. Later, Glenister⁵ noted the presence of the sex chromatin in the trophoblastic cells of an implanting human blastocyst. He also noted it in 6 of 13 human embryos whose gonadal tissue was still in an undifferentiated stage. Park⁶ then studied 33 human embryos, age 36 hours to 24 days, and was able to demonstrate the sex chromatin mass in the trophoblastic cells of 10- to 12-day-old embryos. Determination of gender by the sex chromatin, therefore, permits the assignment of sex in the absence of an embryo. Stated otherwise, the sex of a pregnancy may be established by the determination of gender by the sex chromatin of the fetal portion of the placenta. One may, therefore, undertake to establish the ratio of male to female embryos in abortions by the determination of gender by the sex chromatin content of placental tissue. The preliminary result of such a study constitutes the basis for this report.

Methods and materials

Fresh placental tissue obtained at the time of curettage for the treatment of incomplete abortions was placed in a fixative. Neutral Formalin would do but, since the accuracy of interpretation of the sex chromatin mass depends upon the clarity of nuclear constituents, a specific nuclear fixative was desirable. The one used was Davidson's solution consisting of Formalin (20 parts), 95 per cent alcohol (35 parts), glacial acetic acid (10 parts), and distilled water (35 parts). Each individual specimen obtained was not larger than 1.5 by 1.5 by 1.5 cm. in aggregate. It remained in the special fixative for

not longer than 24 hours lest it become too hard and also to preclude extraction of the desoxyribonucleic acid from the cell nuclei. Paraffin sections were cut at 6 μ . This thickness was chosen because thinner sections would contain an unduly large portion of sliced nuclei, and the sex chromatin mass, if present, might therefore have been encountered less frequently than it ought to have been. A variety of stains such as cresyl violet, cresylecht violet, and thionine have been used for determining gender by the sex chromatin in tissue. However, the Feulgen reaction, with acid hydrolysis for 10 to 20 minutes and with a light green counterstain, gives the best results and was the one used in this study. Actually, the Feulgen reaction is specific for animal nucleic acid; more notably, the stain has an affinity for desoxyribonucleic acid, of which the sex chromatin mass is composed. Though identification of the sex chromatin mass is thus facilitated, the stain does not offer a histochemical differentiation from other nuclear chromatin granules for they, too, are Feulgen-positive. The distinction between the sex chromatin and the other Feulgen-positive chromatin clumps, therefore, remains a morphological one. The sex chromatin mass is much larger (1 μ in diameter) than the other chromatin granules. It is planoconvex in shape with its straight border lying against the nuclear membrane and its convex side bulging into the nucleoplasm.

Since the syncytiotrophoblastic and the cytotrophoblastic cells of the placenta contain a marked amount of other chromatin clumps, identification of the sex chromatin mass (when present) is difficult. These cells are, therefore, not the most suitable for use in the determination of gender by the sex chromatin. Consequently, the cells examined in this study have been the mesenchymal cells which are dispersed throughout the stroma of the villi (Fig. 1). The nuclei of the mesenchymal cells are vesicular and the membranes are distinct. These factors facilitate recognition of the sex chromatin when present. One hundred mesenchymal cells from each specimen were examined under



Fig. 1. Arrow indicates the mesenchymal cells (low power) in the stroma of a villus. These cells were examined in preference to the syncytiotrophoblastic or cytotrophoblastic cells.

oil at an approximate magnification of $\times 1,000$, and the number of cells containing the sex chromatin was tabulated. A specimen with a percentage of 10 or less was considered to be male and one with a percentage of 25 or more was considered to be female (Figs. 2 and 3). This is in accord with the findings of most other workers in the field of determining gender by the sex chromatin. In the current study, the percentages for female tissue ranged from 25 to 81. The percentage count for the male tissue was as high as 8 on two occasions but in the majority of cases it ranged from 0 to 2 per cent.

As a pilot program, one hundred term placentas had been previously assigned sex

by the determination of gender by the sex chromatin of their fetal component. In each instance the sex assigned to a placenta invariably corresponded to the known sex of the baby. Furthermore, most of the abortion specimens in the present study showed both decidual (maternal and therefore female) tissue and chorionic villi. This functioned as a built-in control for the fixation and staining of the specimen. Preliminary and routine examination of the decidua for detection of the sex chromatin, therefore, precluded a false interpretation of maleness (Fig. 4). If the decidual cells failed to show the chromatin mass (female), the section was discarded without an attempt being made to assign sex

Table II. Sex ratio of placental tissue by weeks of gestation*†

	Week of gestation							Total
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	
Male	3	22	72	39	10	3		149
Female	7	13	41	24	7	1		93
Total No. of cases	10	35	113	63	17	4	0	242

*The gestational age was computed in accordance with the recommendation of the National Bureau of Vital Statistics.

†Sex ratio: male to female 160.2:100.

to the fetal portion, the conclusion being that there was a defect in the processing of the material.

Results

To date, 242 abortion specimens have been examined. One hundred forty-nine have been classified as male (chromatin-negative) and 93 as female (chromatin-positive) to give a male to female ratio of 160.2:100 (Table II). No correlation could be found between the sex ratio and the gestational age (Table II).

Comment

Undoubtedly there may be several factors operating to give the sex ratio found in this study. The age, parity, race, and ethnic background of the women from whom the placental tissue was obtained may play a role. Furthermore, the influence of any induced abortions or multiple gestations that may have been present must be considered. At the moment, however, there is no reason to suspect that any of the above factors would be instrumental in obtaining the observed sex ratio of 160.2 to 100, male to female.

Table III. Percentage distribution of perinatal deaths by sex of infant (Kohl)

Sex	Stillbirths	Neonatal deaths
Male	54.7	61.3
Female	45.3	38.7
Number of deaths	237	718

Many studies, the latest by Kohl,⁷ have shown that the male accounts for a greater percentage of the perinatal deaths (stillborn and neonatal deaths) of infants over 1,000 grams (Table III). The results obtained by the determination of gender by the sex chromatin in abortion specimens points out that a similar relationship also holds for early pregnancy wastage. Therefore, the male sustains a greater loss rate in all stages of pregnancy that have been studied. Moreover, the results of the present study with abortions indicate that the accepted secondary sex ratio of 106 to 100, male to female, is not due to a higher loss rate of females in the early months of pregnancy.

Establishment of the primary sex ratio in man is at present impractical. This would require, among other things, the recovery

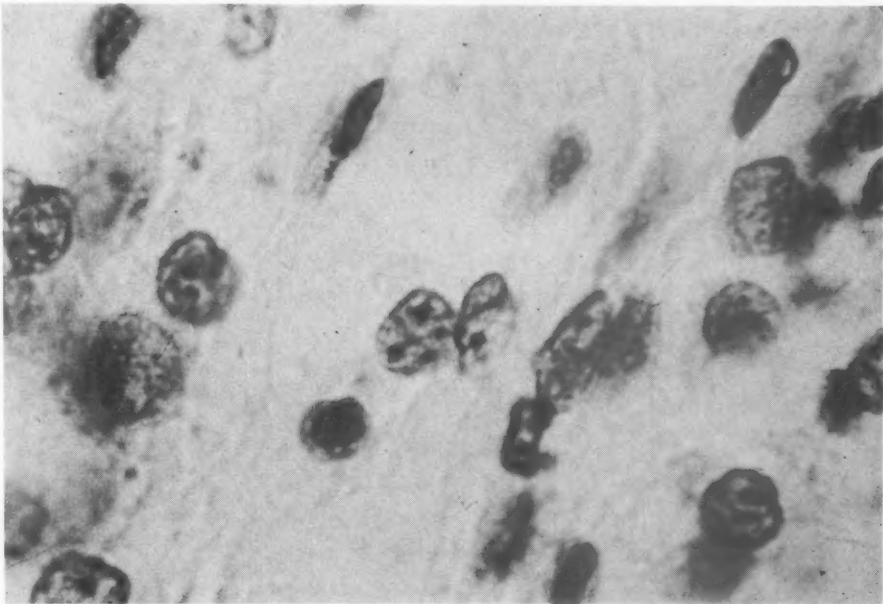


Fig. 2. Mesenchymal cells of a villus showing Feulgen-positive intranuclear chromatin clumps but no sex chromatin mass. Specimen was classified as a male. (Oil immersion. $\times 1,000$; reduced $\frac{1}{3}$.)

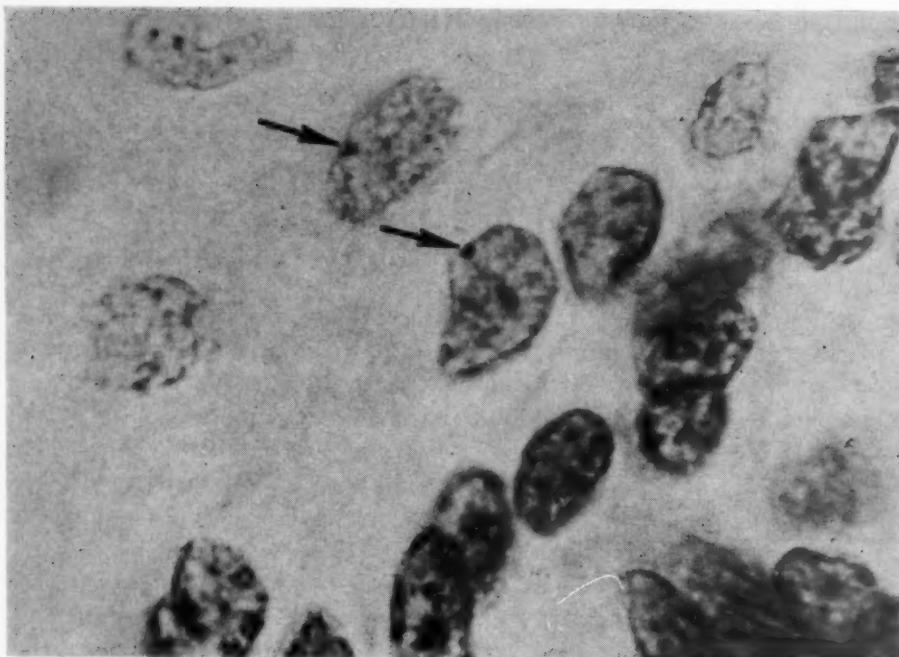


Fig. 3. Mesenchymal cells of a villus (arrows) showing the sex chromatin mass. Note its distinct morphology. Cytotrophoblastic cells, to the right, contain too many chromatin clumps to be suitable for determining gender by the sex chromatin. Specimen was classified as a female. (Oil immersion. $\times 1,000$; reduced $\frac{1}{4}$.)



Fig. 4. Stromal cell and gland cell of decidua containing the sex chromatin mass. The decidual cells were routinely screened for the presence of the sex chromatin mass. Its absence reflected improper fixation and/or staining and the section would therefore be discarded. (Oil immersion. $\times 1,000$; reduced $\frac{1}{4}$.)

and determination of sex of zygotes which fail to cleave and blastocysts which fail to implant. However, with the additional data now available as a result of the determination of the sex of embryos in abortions, an approximation of the primary sex ratio may be attempted which was heretofore not possible. Accepting the incidence of abortions to be 10 per cent, the secondary sex ratio to be 106:100, and the sex ratio of abortions to be of the order of 160:100, the combined ratio, that is, the ratio for all pregnancies studied would be 111 to 100, male to female.* Unless one postulates that the sex of uncleaved zygotes and nonimplanting blastocysts is so predominantly female as to reverse this ratio, 111 to 100 may represent a close approximation of the primary sex ratio in man. Why an egg should be fertilized more frequently by a Y-bearing than an X-bearing sperm when it is theoretically exposed to an equal number of each would then have to be explained.

Conclusions

Barr's discovery of a morphological difference between male and female on the basis of the sex chromatin content of resting nuclei permits the determination of the sex of embryos in abortions. To date, 242 abortions have been assigned sex by the technique of determining gender by the sex chromatin of placental tissue. Though it is too small a series to be conclusive, the preliminary result of a male to female ratio of 160.2:100 indicates that it is the male who makes up the greater part of early pregnancy wastage as he does the perinatal mortality of infants over 1,000 grams. The secondary sex ratio of 106 to 100, male to female, is, therefore, not consequent upon a greater loss of females in early pregnancy.

From the data now available, one may theorize by employing a weighted mean that the primary sex ratio in man approximates 111 to 100, male to female.

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*The weighted mean of 111:100 is derived as follows: in one tenth of pregnancies the sex ratio is 160:100 while in nine tenths the ratio is 106:100. Therefore, $\frac{(160 \times 1) + (106 \times 9)}{10}$ gives the ratio for all pregnancies.

Abortions: ten years' experience at Kansas University Medical Center

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THIS paper is a review of the abortions that were treated at the Kansas University Medical Center from Jan. 1, 1948, through Dec. 31, 1957. This review includes those cases in which the fetus weighed 500 grams or less regardless of the period of gestation as figured by the date of the last menstrual period.

Table I gives the general data. The figure of one abortion for each 15.8 deliveries is probably incorrect for the over-all picture as many patients who had abortions were never hospitalized; it merely represents the ratio between deliveries and abortions in this hospital. Javert and Finn¹¹ quote a figure only slightly higher—7.9 per cent. It is extremely difficult to obtain accurate figures of the frequency of abortion in any country. Dunn⁵ estimated one abortion to every 5.6 confinements for urban areas and one abortion to every 9.4 confinements for rural areas. The cause for the higher figures in the city is difficult to determine. Such stated reasons as a higher incidence of gonorrhea and accessibility to the abortionist are probably incorrect. Many authors have expressed the opinion that a large number of abortions occur in the first weeks of gestation and are misdiagnosed as delayed or profuse menstruation. Javert¹⁰ has estimated that about 10 per cent of the calculated

4 million pregnancies in America in 1955 ended in spontaneous abortion. One has no way of knowing how many additional pregnancies ended by criminal abortion. In a conference sponsored by the Planned Parenthood Federation of America, Inc., in New York in 1956, in which many of the outstanding authorities of the United States as well as of other countries took part, one speaker estimated that there were two thirds of a million criminal abortions each year in the United States. Another statement made during this same conference was "a plausible estimate of the frequency of induced abortions in the United States could be as low as 200,000 or as high as 1,200,000 per year."² This certainly points out how difficult it is to get any idea of the over-all incidence. Many authors, such as Rock,¹³ Kopp,¹⁶ Stix,¹⁸ and Taussig,¹⁷ feel that as many as two thirds of all abortions may be induced. Davis,⁴ in an article published in 1950, estimated that 90 per cent of abortions in England were induced, and that, in the majority of the cases, the induction was by the patient, herself. However, Gebhard, Pomeroy, Martin, and Christenson,⁶ from the material collected by the Institute for

Table I

Total No. of patients	890
Negro	538
White	352
Total No. of abortions	927
Total No. of deliveries	14,630*

*One abortion for each 15.8 deliveries, or an incidence of 6.3 per cent.

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Table II. Age incidence

Age (years)	Abortions	
	No.	%
20 or under	148	17
21-30	502	56
31-40	217	24
41 or over	23	3

Table III. Previous abortions

Previous abortions	No.	%
None	550*	61.8
One	224	25.2
Two	75	8.4
Three or more	40	4.5
Unknown	1	0.1

*Includes 143 primigravidas.

Sex Research formerly headed by the late Dr. Alfred Kinsey, found that less than one per cent of operative abortions were self-induced. By operative abortion they refer to insertion of any instrument or drug or other substance into the uterus or the os of the cervix. Rock¹³ stated that an abortion rate of 25 per cent of pregnancies is a conservative estimate.

Table II shows a breakdown of the occurrence of abortions by age groups. Table III gives the number of previous abortions. The greatest number of abortions by any one patient was 11.

Table IV shows the gestational period of these abortions. The figure of 70.9 per cent agrees closely with that of Hamblen⁷ and Hertig and Edmonds,⁸ who have found that roughly three fourths of abortions occur in the first 3 months of gestation.

Table V shows the causes of abortions divided into four categories: unknown, physical, fetal, and maternal.

There were 122 cases which were attributed to physical causes (Table VI). There were 33 cases in which a definite history of criminal induction was obtained. Methods of induction given were: stem pessary, 8; catheter, 2; rubber tube, 1; garden hose, 1; uterine pack, 1; quinine, 1; not stated, 19. There were 33 cases in which strong suspicion of criminal induction was

present but a definite history was not elicited, making a total of 66 cases of probable criminal abortion. Forty-six cases fell into the category of trauma, such as intercourse, fall, overexertion, straining, auto trips, and laxatives. There were 10 cases of surgical causes. In 3 patients the diagnosis of pregnancy was missed; one of these had a dilatation and curettage; one had a dilatation and curettage and conization, and one had a supracervical hysterectomy. There were 4 cases of abortion following operative procedures, such as appendectomy. There were 2 cases of hysterotomy; one was for a missed abortion; the other was a therapeutic abortion for chronic glomerulonephritis. There was one total hysterectomy for severe hypertensive cardiovascular disease.

In 94 cases the cause of abortion was fetal in origin (Table VII). Fifty-eight were classified as ovular and included 54 blighted ova and 4 hydatidiform degeneration. There were 20 premature ruptures of the membranes. In the placental category there were 10 premature separations of the placenta, one placenta previa, and one infarction of the placenta. Miscellaneous fetal causes included 2 congenital abnormalities and 2 Rh incompatibilities.

There were 67 cases in which the cause of abortion was thought to be maternal (Table VIII). The basal metabolic rates on these patients in the "hypothyroidism

Table IV. Gestational period

Length of gestation (months)	No.	%
Three or under	657	70.9
Four	140	15.0
Five	88	9.5
Six or over	19	2.2
Unknown	23	2.4

Table V. Causes of abortion

Cause	No.	%
Unknown	654	69.8
Physical	122	13.0
Fetal	94	10.0
Maternal	67	7.2

Table VI. Physical causes of abortion (122 cases, 13 per cent)

Cause	No.	%
Criminal (?)	66	54.1
Trauma	46	37.7
Surgical	10	8.2

Table VII. Fetal causes of abortion (94 cases, 10 per cent)

Cause	No.	%
Ovular	58	61.7
Membranes	20	21.3
Placental	12	12.8
Miscellaneous	4	4.2

Table VIII. Maternal causes of abortion (67 cases, 7.2 per cent)

Cause	No.	%
Hypothyroidism	32	47.7
Infections	17	25.4
Miscellaneous	18	26.9

group" ranged from a plus 5 to a minus 17. The "infection" category included one case of mumps, 2 cases of upper respiratory infection, one case of diphtheria, one case of cystitis, 5 cases of pyelitis, one case of endometritis, 4 cases of influenza, and 2 cases of acute infection, site and type not stated. The cases of miscellaneous causes included 6 cases of uterine fibroids; one case of obesity; one of hyperemesis; 2 of diabetes; one of secondary ovarian failure; one of pregnancy within a short time after delivery; one of serious heart disease plus pneumonia; one of cervical laceration; 2 of severe asthma; one of emotional factors; and one of arcuate uterus.

By far the greatest category was that of the unknown, totaling 654 cases, which is 69.8 per cent of the total number of abortions. This emphasizes the need of more effort being directed toward finding the cause of the abortion. If the cause is unknown there is little hope in determining whether or not the abortion could have been

prevented and, thus, arriving at a rational method of therapy.

Tissue from 862 of the 927 abortions was submitted to the pathology laboratory. Table IX shows the pathologic findings. In the cases where definite products of conception were not diagnosed, a history of having passed fetal products was obtained.

It is interesting to note that such a large percentage of cases had tissue submitted to the pathology laboratory for analysis and certainly indicates an earnest effort on the part of the clinician in getting tissue to the pathologist. It should be stressed, however, that it is important for the clinician to submit all of the tissue. Perhaps the pathologist could be criticized for not examining the tissue more carefully in an attempt to find a cause for the abortion. Most of the cases reported here under "pathologic report showing definite products of conception" were reported simply as placental tissue, fetus, etc. Hertig and Edmonds⁸ have demonstrated that the absence of all or most of the embryo is the most common single finding in complete spontaneous abortion. Hertig and Rock⁹ found 43 per cent of their very, very young embryos obtained from

Table IX. Pathologic report (927 cases)

Finding	No.	%
Products of conception	732	79.0
Acute and/or chronic endometritis	91	9.8
Miscellaneous	39	4.2
No report	65	7.0

Table X. Morbidity* (204 cases, 22 per cent)

<i>Complete abortion</i>	
Total patients	376 (41%)
Morbid	92 (24.5%)
Average days in hospital	4.6
<i>Incomplete abortion</i>	
Total patients	551 (59%)
Morbid	112 (20.3%)
Average days in hospital	6.0

*Temperature 100.4° F. on admission or at any time 24 hours postoperatively.

fertile women prior to their first missed menstrual period were abnormal. In view of these findings it behooves both the clinician and the pathologist to examine the tissue very carefully, especially in early abortion. It would seem from the careful work of such men as Mall and Meyer,¹² Streeter,¹⁵ Rock and Hertig,^{9, 13, 14} Edmonds,⁸ and Javert¹¹ that the earlier in pregnancy the abortion takes place the higher the incidence of pathologic ova.

The days in hospital ranged from 1 to 33 with an over-all average of 5.5 days.

Table X compares the morbidity of the complete and the incomplete abortions. The abortion was defined as being complete if the patient expressed the products of conception from the uterus entirely on her own, while if any assistance was required for removal of any part of the conceptus from either the uterine cavity or cervix the abortion was classified as incomplete.

There was approximately 4 per cent less morbidity in the incomplete group than there was in the complete group. Of the 112 morbid patients in the incomplete group, 81 were morbid on admission, had a dilatation and curettage or manual removal of the fetal structures, and had no further morbidity. There were 6 patients of this group who were morbid on admission, had a dilatation and curettage, and were also morbid postoperatively. There were 25 patients who were not morbid on admission, had a dilatation and curettage, and then developed morbidity postoperatively. The average number of days in the hospital for the incomplete group was 6, or 1.4 days longer than the complete group. The number of days after abortion until the patient had a dilatation and curettage or manual removal of fetal structures ranged from 0 to 180 days, with an average of 7.5 days. The number of days in hospital after dilatation and curettage or manual removal of fetal structures ranged from 0 to 22 days with an average of 3.2 days.

There seem to be two main schools of thought concerning the treatment of inevitable or incomplete abortions. According

to the first view, if left alone the uterus will ultimately empty itself and if allowed to do so the patient is subjected to the least possible risk. Some advocates of this idea believe the mortality is two times as high with active therapy as with the conservative treatment. These results, however, were obtained before the days of specific chemotherapy. This treatment predisposes to increased blood loss and also requires many hospital beds, for it may take several weeks for the abortion to be completed.

The second view holds that all inevitable and incomplete abortions which are not rapidly and spontaneously completed should be treated by surgical evacuation of the uterus. This method of treatment for the most part will decrease the over-all blood loss, and it requires fewer beds since the patient stays in the hospital a relatively short time. Carston and Stallworthy,³ of Great Britain, and recently, Brown and Hanisch,¹ of this country, have reported excellent success by using the so-called radical method.

If the average patient stays in the hospital 3.2 days after surgical evacuation of the uterus, it would seem logical to operate immediately in order to shorten the over-all hospital stay. I think this approach certainly should be tempered with a little common sense in that sufficient time should be allowed in which to get the patient's temperature down by use of antibiotics if she is febrile, and to replace fluids and blood if indicated. As suggested by some, intravenous Pitocin might be used in an attempt to empty the uterus. Certainly the patient should be in the best condition possible before the operation is performed. If excessive hemorrhage is present, of course, immediate intervention is in order. Here again, careful clinical judgment must be exercised if the patient is septic. Perhaps under these circumstances a uterine pack is the method of choice. Removal of the pack 24 hours later will usually bring with it the remaining placental tissue. I believe this general policy has been followed at the Kansas University Medical Center in

the past and apparently has produced good results, as our morbidity in the incomplete group is actually slightly better than that in the complete group. If the argument by the conservative followers of marked increase in hazard to the surgical approach were true, one would expect the morbidity of the incomplete group who were all treated surgically to be much greater than the complete group; however, these figures do not bear this out. The delay in intervention while waiting for the uterus to empty spontaneously may account for the higher incidence of morbidity in the complete group. It would seem logical that if there is any doubt as to whether the abortion is complete or not, a dilatation and curettage would be less likely to produce morbidity than would waiting.

The causes of morbidity were classified as unknown, sepsis, and miscellaneous (Table XI). In the "sepsis" category there were 3 cases in which a positive blood culture was obtained; one of these was streptococcal infection and another an enterococcus; in the third the identity of the bacteria was not given. There were 13 cases of acute endometritis, etiology unknown, and 1 case of acute endometritis due to *Escherichia coli*. Miscellaneous causes of morbidity included 1 case of pyelitis, 3 of cystitis, one of intravenous reaction, 2 of pneumonia, 2 of "flu," one of infected secundines, one of abscessed tooth, and one of meningitis, etiology unknown.

Table XII gives data on hemoglobin and transfusions.

Of the 890 patients in this series, 121 (13.6 per cent) had had some type of previous gynecologic operation. There were 85 minor and 36 major operations. This figure of 13.6 per cent for previous gynecologic operations does not seem excessive.

Table XI. Causes of morbidity

Causes	No.	%
Unknown	175	85.8
Sepsis	17	8.3
Miscellaneous	12	5.9

Table XII. Blood loss

Hemoglobin on admission (grams)		
Average		10.8 (76%)
Range	3.7 (24%)	16.9 (109%)
Transfusions		
One		119 (45.9%)
Two or more		140 (54.1%)

During this same period of time there were 52 patients hospitalized for threatened abortion who subsequently went to term. This figure does not represent the total number of patients with threatened abortions who went to term, as many of the threatened abortions were treated on an outpatient basis.

Summary

Nine hundred twenty-seven abortions occurring in 890 patients treated at the Kansas University Medical Center from Jan. 1, 1948, through Dec. 31, 1957, have been reviewed. During the same period of time, 14,630 deliveries occurred. This gave an incidence of one abortion for each 15.8 deliveries, or 6.3 per cent.

The predominant number of the abortions in this series occurred in the 21 to 30 age group.

Sixty-two per cent of the patients had had no previous abortions, 25 per cent had had one previous abortion, 8 per cent had had two previous abortions, and 5 per cent had had three or more previous abortions.

Seventy-one per cent of the abortions occurred during the first 3 months of gestation. In 70 per cent of the cases no cause of abortion was given. In all but 65 cases tissue was studied.

The over-all average number of days in hospital was 5.5. In the group with complete abortion the average number of hospital days was 4.6, and in the group with incomplete abortion, 6 days.

There were 376 complete abortions and 551 incomplete abortions; 24.5 per cent of the complete group and 20.3 per cent of the incomplete group were morbid; 27.9 per cent of the patients required transfusions.

No correlation could be made between previous gynecologic surgical procedures and the incidence of abortions.

Conclusions

Since in almost two thirds of the cases no cause of the abortion was given, more attention should be directed toward finding the cause. This responsibility lies with both the clinician and the pathologist.

The method of treatment of the incomplete abortion as practiced at Kansas University Medical Center has shown good results. We may conclude that it is safe to intervene in the incomplete abortion if clinical judgment is exercised in getting the patient in good condition preoperatively.

The over-all morbidity might be improved by early surgical intervention in cases where there is a question of whether or not the uterus is completely emptied.

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Vascular collapse complicating septic abortion

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ABORTION complicated by sepsis is a common gynecologic problem which, in the antibiotic age of today, leads to very little mortality. However, when the infecting organisms are of a particular virulence or when they are introduced in gross numbers from without, as in criminal abortion, the sepsis may lead to bacteremia and vascular collapse. Once this stage is reached, the mortality may approach 50 per cent even today. It is the purpose of this paper to present 6 cases of abortion with septicemic shock and to evaluate the physiologic basis of present-day treatment to see if anything further can be done to save more of the lives of these unfortunate women.

Description of entity

The appearance of vascular collapse without significant blood loss in a patient with septic abortion establishes the diagnosis. The shock is preceded by shaking chills and a spiking temperature which may reach very high levels. All the signs and symptoms of shock are present, including hypotension, pallor, rapid, thready pulse, diaphoresis, and frequently a falling temperature. The patient presents a picture of overwhelming infection and toxemia. Renal,

hepatic, and cardiac complications should be anticipated.

Shock associated with infection is not a new complication. Boise,¹ in 1896, described the problem of differential diagnosis of shock, hemorrhage, and sepsis, and Ebert and Stead,² in 1941, discussed circulatory failure in fulminating infections. In recent years large numbers of patients with bacteremia complicated by vascular collapse have been reported.³⁻¹¹ One series³ included 2 fatalities from septic abortion and shock. Large series of patients with septic abortions have recently been reported¹²⁻¹⁵ but only Studdiford and Douglas¹² have emphasized the complication of septicemic shock in these patients.

Case reports

Case 1. P. S., a 29-year-old white patient, para 4-0-0-4, was admitted to St. John's Hospital at 12 weeks' gestation with a history of attempting to induce an abortion with "slippery elm" a few days prior to admission. The previous day she noted chills and fever. Low abdominal tenderness was present, the cervix was closed, the fundus was moderately enlarged and all the pelvic organs were tender. The clinically significant features are seen in Fig. 1. Collapse occurred 11 hours after admission and persisted for one and one-half hours in spite of blood replacement therapy. A blood culture was sterile. Dilatation and curettage was performed approximately 4 hours after the onset of shock in spite of the patient's precarious condition. Levophed was necessary to maintain her

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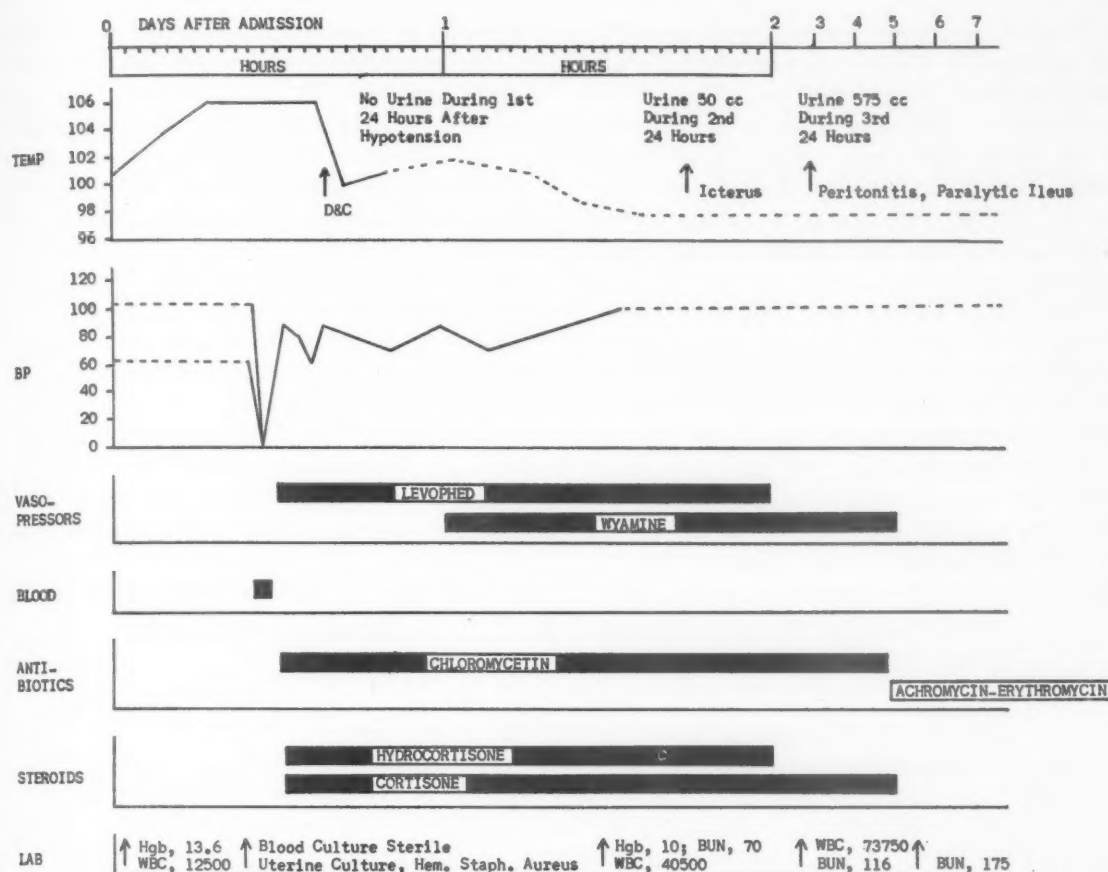


Fig. 1. Case 1.

blood pressure for approximately 36 hours. Toxic hepatitis, uremia, and delayed manifestations of peritonitis attested to the severity of her illness. The jaundice was noted on the second day, the total serum bilirubin being 8.6 mg. per cent. Convalescence was complicated by a slough at the site of the Levophed infusion and a subphrenic abscess which required drainage 3 months later.

Case 2.* P. V., a 36-year-old white patient, para 4-0-2-4, was admitted to the Charles T. Miller Hospital at 20 weeks' gestation with a history of chills and fever for 4 hours. Rupture of membranes had occurred 3 hours prior to admission. The uterine fundus was 20 cm. above the symphysis pubis with moderate tenderness. An x-ray examination of the abdomen showed a fetal skeleton. The patient's course is illustrated in Fig. 2. The episode of collapse oc-

curred 56 hours after admission and was accompanied by moderate bleeding. She had been on antibiotic therapy for 24 hours. A 300 gram fetus was aborted shortly thereafter, the placenta being retained. The patient was in shock 4 hours in spite of 3 units of blood. A blood culture was sterile. A Levophed infusion was necessary for 72 hours. Urinary output was adequate. A history of interference was not elicited; the pregnancy was further advanced than our other cases. Her recovery was complicated by abscess formation at the site of the venous cut-down due to hemolytic *Staphylococcus aureus*, coagulase positive, which was, fortunately, sensitive to Albamycin.

Case 3. M. B., a 31-year-old white patient, para 3-0-1-3, was admitted to the Charles T. Miller Hospital at 8 weeks' gestation by history. She had had fever, chills, vaginal bleeding, and low abdominal tenderness for 3 weeks. She attempted to induce an abortion several days prior to the initial febrile episode. Shortly after

*This case is presented with the permission of Albert F. Hayes, M.D., St. Paul, Minnesota.

the onset of symptoms she was given an injection of penicillin by another physician. On admission a tender mass was palpated 8 cm. above the symphysis pubis. The cervix was closed and all the pelvic organs were tender. The patient's course is depicted in Fig. 3. An important feature was that there was a long delay in the appearance of vascular collapse during which time she received inadequate therapy. On admission a blood culture was taken, and it grew *Proteus* and *coli-aerogenes*; treatment with Chloromycetin was begun. Collapse occurred 8 hours after admission. She responded well to therapy, and urinary output during the first 24 hours was approximately 2,000 ml. The fluid intake was approximately 3,000 ml. A 10 gram fetus was expelled with retention of the placenta shortly after the onset of shock. Pulmonary edema with an intensification of the shock

in spite of continuous metaraminol bitartrate (Aramine) infusion occurred 16 hours after the initial episode. The blood pressure then responded well to Levophed, but pulmonary edema persisted and the patient's condition rapidly deteriorated. Autopsy showed acute suppurative pelvic inflammatory disease and peritonitis as well as ovarian vein thromboses. Blood and uterine cultures grew *Proteus* and *coli-aerogenes*.

Case 4. H. L., a 40-year-old white patient, para 4-0-1-3, was admitted to Ancker Hospital at 13 weeks' gestation. She had been well until 10 days prior to admission when slight bleeding occurred. Eight hours before admission she noted chills, and her temperature was 105°. Moderate vaginal bleeding, abdominal cramps, and faintness began 4 hours prior to admission. On admission she was irrational, cyanotic, and

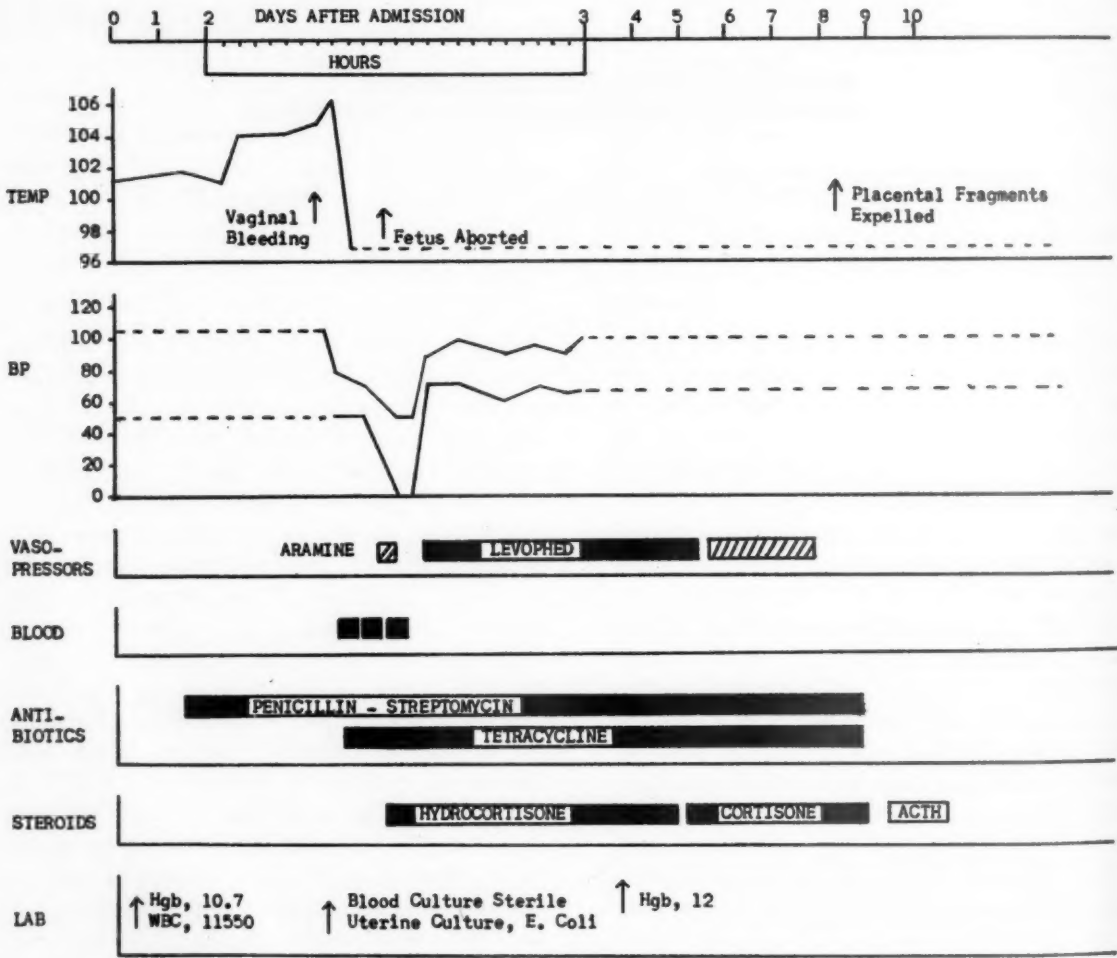


Fig. 2. Case 2.

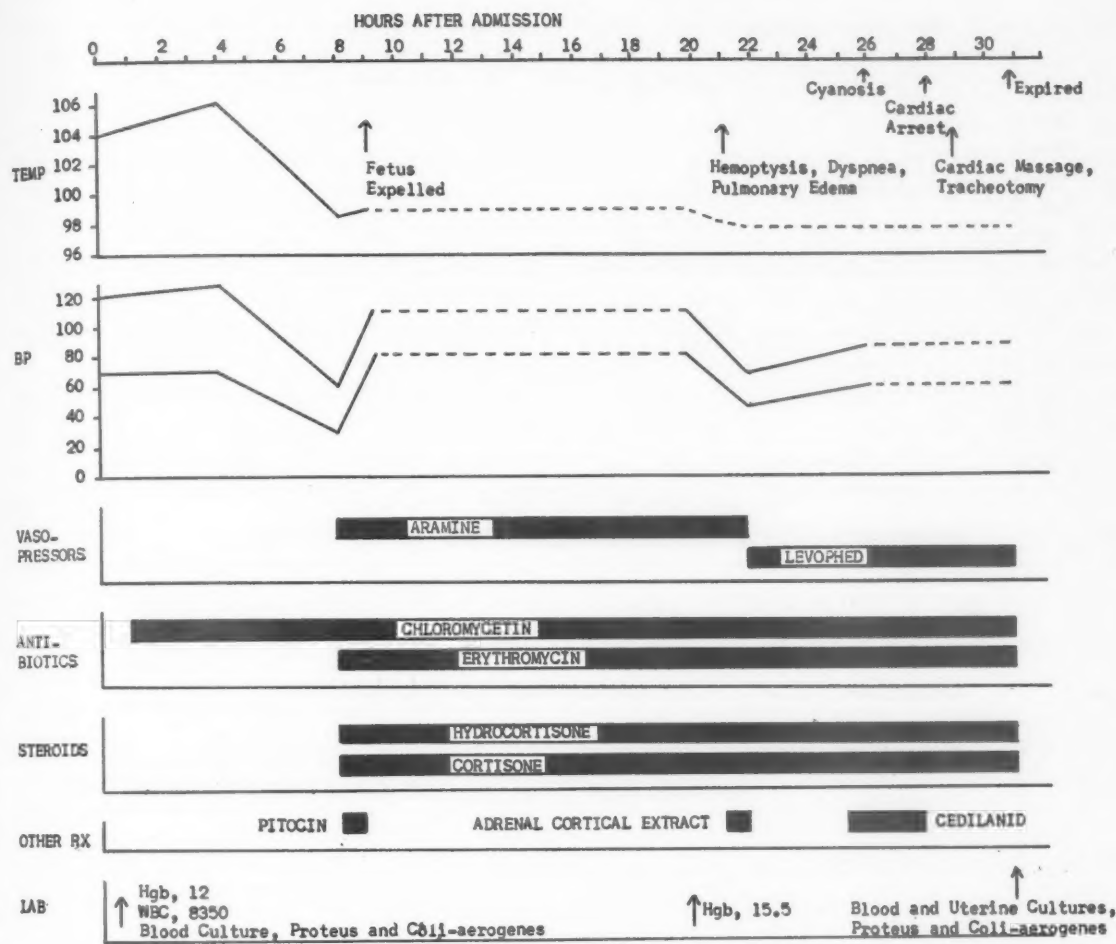


Fig. 3. Case 3.

in clinical shock. Low abdominal tenderness was present and the uterus and adnexa were tender, the former being enlarged and soft. No history of interference was obtained. Her course is represented in Fig. 4. Collapse persisted for 2 hours but then responded well to therapy which included one unit of blood and a plasma expander. Two hours after admission the placenta was removed from the endocervical canal and it was felt the abortion was complete. Continuous Aramine infusion was necessary for 20 hours. Blood and uterine cultures grew *Escherichia coli*.

Case 5. L. G., a 36-year-old white patient, para 2-0-0-2, was admitted to the Charles T. Miller Hospital at 12 weeks' gestation. Fever, chills, low abdominal tenderness and pain, and vaginal bleeding had been present for 4 days. She later admitted to criminal interference with "slippery elm" 5 days prior to admission. The

cervix was closed, the fundus was first degree retroverted and slightly enlarged, and there was tenderness of all the pelvic organs. The significant features of the patient's course are illustrated in Fig. 5. Broad spectrum antibiotics were begun. Collapse occurred 11 hours after admission, responding in one to 2 hours to therapy. Blood culture was sterile. Approximately 3½ hours later the uterus was emptied surgically. Bradycardia and electrocardiographic evidence of toxic myocarditis were noted within 24 hours of the initial collapse. These persisted for 6 days. The various antibiotics were discontinued between the sixth and ninth days, and on the tenth day another febrile episode complicated by vascular collapse occurred. This episode also responded well to treatment. Bradycardia again occurred and persisted for 4 days. Late complications included bilateral tubovarian abscesses and bacterial endocarditis.

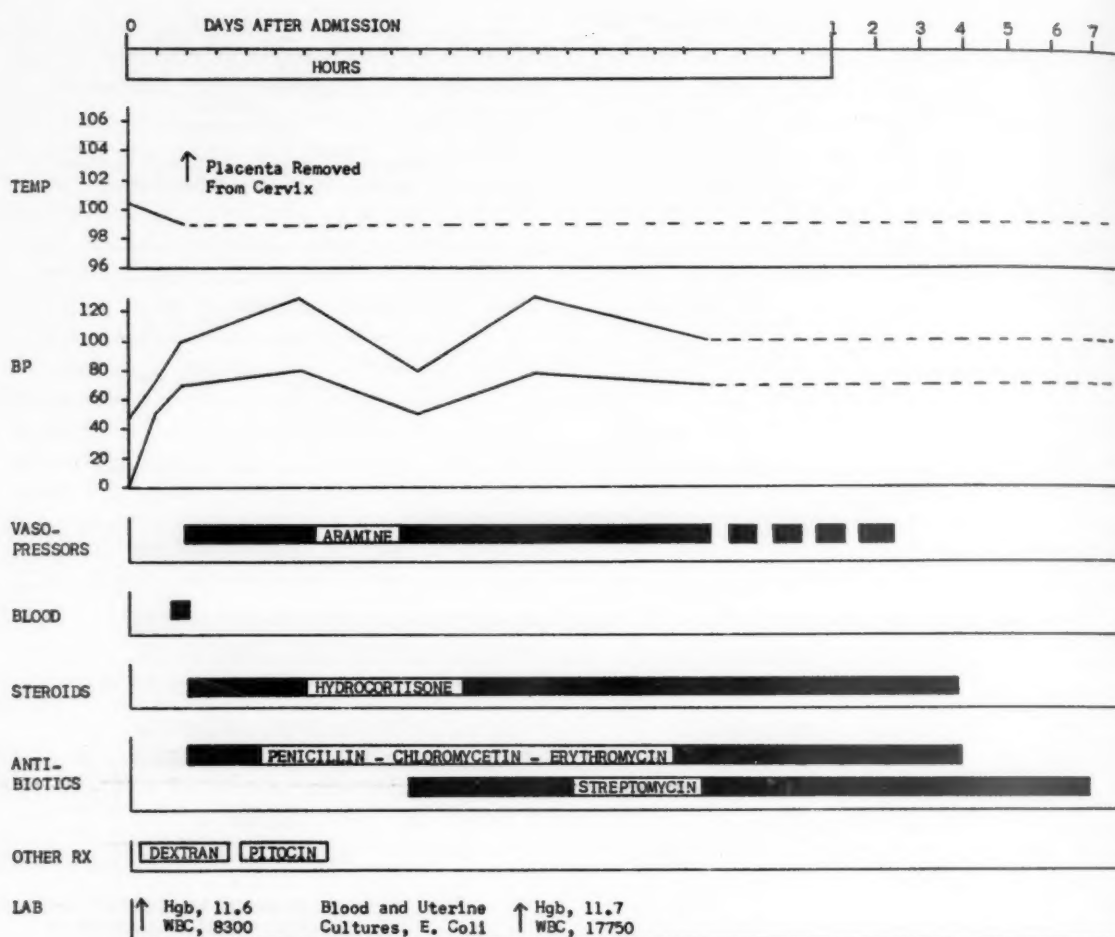


Fig. 4. Case 4.

Case 6. M. Z., a 26-year-old divorced white patient, para 4-0-1-5, was admitted to Ancker Hospital stating an attempt had been made to induce abortion by a high pressure tap water douche 24 hours previously. Later information revealed similar attempts had been made for at least a week prior to admission. By history the duration of gestation was 6 weeks. Vaginal bleeding, low abdominal pain, weakness, vertigo, and diarrhea had been present for 24 hours. Examination showed the patient to be alert. Low abdominal and rebound tenderness was present as was splinting of the lower abdominal muscles. Placental tissue was in the vagina; the cervix was clean; the fundus was the size of an 8 weeks' gestation; no adnexal masses were present, and all the pelvic organs were tender. Her course is illustrated in Fig. 6. Massive parenteral antibacterial and steroid therapy was begun. Unfortunately, antibiotic therapy had

been initiated 30 minutes prior to the taking of the blood culture. Evacuation of the uterus was performed with a few minutes of anesthesia. Subsequently her condition improved until 5 hours after the curettage when sudden, irreversible shock occurred which was unresponsive to increasing amounts of Levophed. At autopsy she was found to have generalized, massive, purulent peritonitis with large collections of exudate which were sterile.

Pathologic physiology

Vascular collapse causes functional and organic changes in various systems. Decreased cardiac output is the result of hypovolemia and insufficient coronary blood flow.¹⁶⁻²⁰ Myocardial failure results in a further decrease of cardiac output, compounding the problem. The marked de-

crease of renal blood flow is accounted for by the hypotension and renal vasoconstriction.²¹ Experimental hemorrhagic shock produces abnormal electroencephalograms and a decrease of cortical oxygen tension.²²

The mechanisms involved in response to shock of any origin have been investigated for many years and are still basically unsolved. Shock can be the result of a combination of factors. Fine and associates^{23-26, 30} showed that bacteria play a role in irreversible hemorrhagic shock. Animal experiments with hemorrhagic shock have been used extensively to investigate the factors in "irreversibility." Generalized vasoconstriction occurs rapidly in all types of shock and redistributes a large volume of blood to those structures whose function is

vital for immediate survival. The beneficial influence of the initial vasoconstriction prevents the development of a hemodynamic crisis. Evidence is accumulating that prolonged vasoconstriction in the less essential organs leads to production of lethal factors. The principal autopsy findings of dogs dying of irreversible hemorrhagic or endotoxic shock are remarkably similar. Hemorrhagic necrosis of the bowel is uniformly present.²⁷⁻³⁰ It is felt that this is due to vasoconstriction and oligemia of the gut and is responsible for an increase in hematocrit and plasma hemoglobin and a decrease of plasma volume.^{29, 31} The similarity of vascular collapse due to bacterial endotoxin and other causes, such as anaphylaxis, suggests a common factor,³²⁻³⁴ resulting in dam-

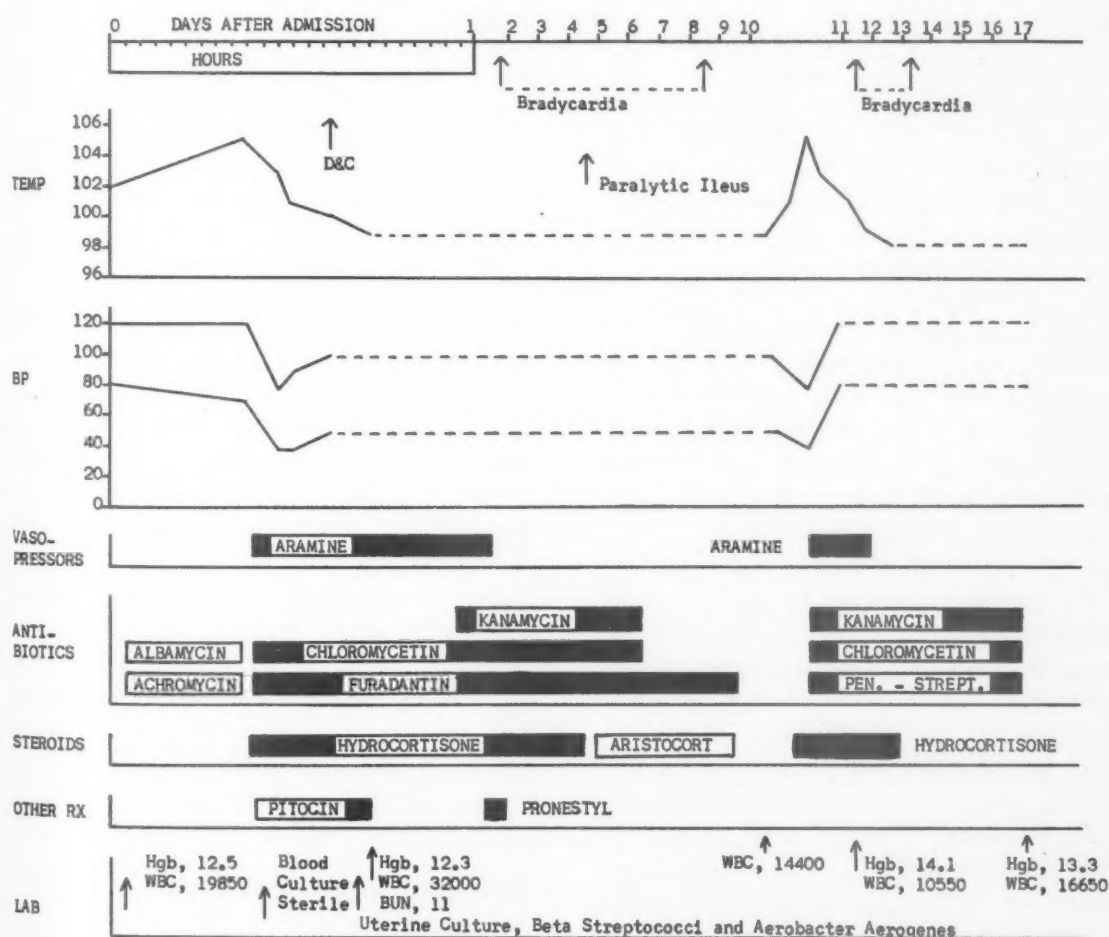


Fig. 5. Case 5.

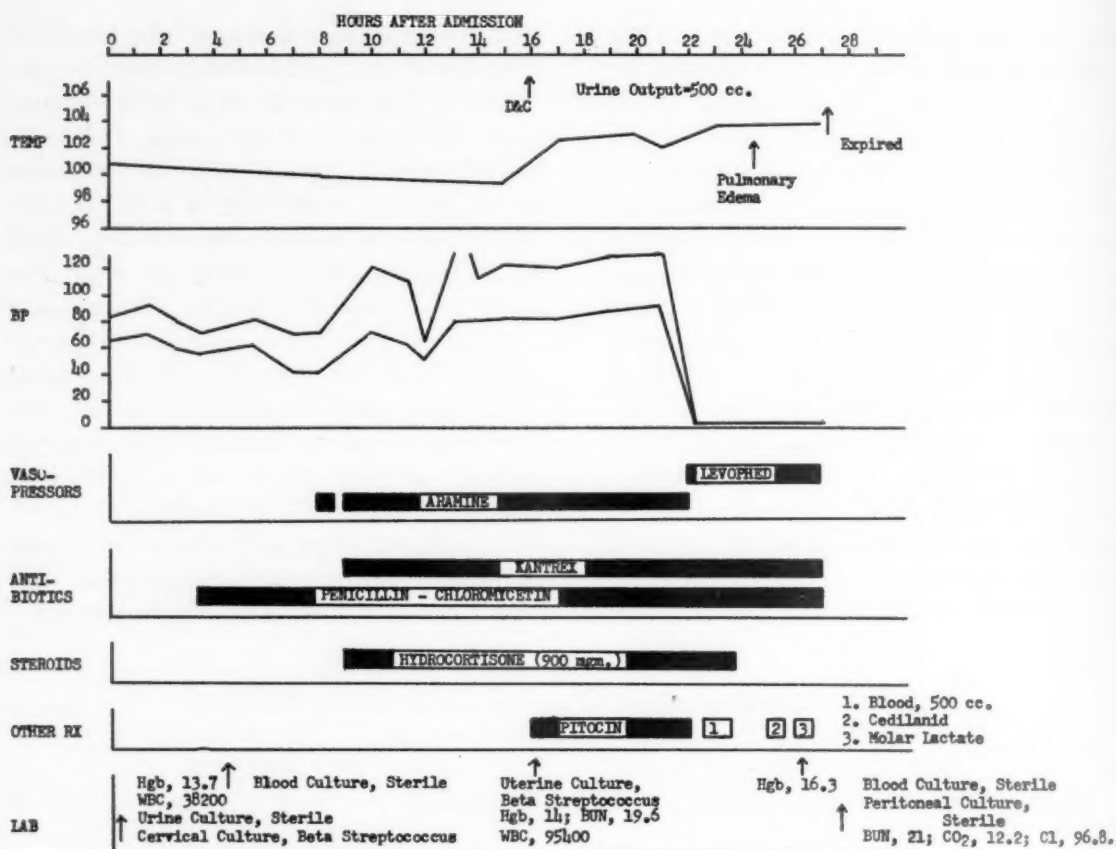


Fig. 6. Case 6.

age to the reticuloendothelial system.^{30, 35, 46} Humoral factors originating primarily in the kidney and liver have been implicated by Shorr and co-workers.^{36, 37} Much work has been concerned with the production of shock by bacterial toxins.^{32, 38-45} It has been demonstrated that the endotoxin of *E. coli* is carried in the plasma and is concentrated in the reticuloendothelial system.^{40, 41, 46} In experimental hemorrhagic shock, other investigators have debated the role of increased portal vein pressure and intestinal congestion.^{27, 28, 31, 47-52} Decrease of venous return to the heart and cardiac output are constant occurrences in endotoxic shock and Weil, MacLean, Visscher, and Spink^{32, 43} have demonstrated that in dogs these changes are due to pooling of blood in the portal circulation, particularly the intestine, with an increase of portal vein pressure.

They have demonstrated that the effect of the endotoxin is not on the heart or central nervous system.^{42, 44, 45} Essex and Thomas^{53, 54} showed that certain toxins in dogs caused contraction of the hepatic venous vasculature with resultant arterial hypotension, hepatic congestion, and increased portal vein pressure. It has been shown that mechanical obstruction of hepatic veins causes hypotension with a decrease of venous return to the heart.⁵⁵ This hypotension occurs before the congested area can become anoxic. However, Lillehei and MacLean²⁹ feel that in endotoxic shock hepatic factors are of less importance than congestion and necrosis of the bowel mucosa.

Physiologic basis for treatment

In recent years vasopressor drugs have been used in treating all types of refrac-

tory vascular collapse and in particular that type caused by bacterial endotoxin.^{5, 8, 17, 21, 56-58} The most effective drugs have been norepinephrine and metaraminol. Experimental studies⁵⁹⁻⁶¹ have shown that vaso-pressor drugs increase venous return to the heart and may have a dilating action on the hepatic veins.⁶² In the normotensive patient, norepinephrine has a renal vasoconstrictor action,^{21, 63} but in shock it increases renal blood flow, glomerular filtration rate, and urinary output. In normotensive dogs the renal blood flow is only slightly decreased with metaraminol as compared to norepinephrine.²⁶ Metaraminol has been shown to increase myocardial contractibility in normal and anemic dogs and in dogs with myocardial failure due to coronary insufficiency.⁶⁵ Bradycardia occurs occasionally; coronary blood flow is increased; no abnormalities of ventricular rhythm or contraction occur.^{58, 66} Norepinephrine further decreases coronary vascular resistance in the dog with hemorrhagic hypotension and increases coronary blood flow. Peripheral blood flow is increased even though peripheral vascular resistance is increased.²⁰ Similar studies have shown that norepinephrine increases myocardial oxygenation.¹⁹ These drugs would seem to have a physiologic action on the heart, kidneys, and liver in a patient with bacterial shock. However, their effectiveness may be decreased by acidosis. Infusion of sixth molar lactate solution in these patients may be beneficial.^{17, 67}

Some reports on the use of vasopressor amines in shock have not been favorable.⁶⁸ The damage to less vital organs in shock due to prolonged vasoconstriction, as referred to previously, may be accelerated by pressor drugs.⁶⁹ Recently, these drugs have been found either to have no effect or to potentiate the shock by increasing vasoconstriction in endotoxic shock in dogs.²⁹ The possibility that the vasopressor amines are responsible for an increasing incidence of patients with liver necrosis has been suggested.⁷⁰ In view of these findings the use of vasopressor agents should be restricted to

the least amount necessary for maintenance of renal function.

Recently sympathetic nervous system blocking agents have been used in the treatment of experimental hemorrhagic shock. The results of these studies are conflicting.^{22, 69, 71-84} Noyes and associates,⁸⁵ in experiments in mice with various bacterial endotoxins, found protection with chlorpromazine and Dibenzylamine. A recent study in dogs confirmed these findings.²⁹ The beneficial effects of these and related drugs may be explained by the findings of Thomas⁸⁶⁻⁸⁸ that endotoxin adversely intensifies the local action of epinephrine. The efficacy of sympathetic nervous system blocking agents in humans has not been reported.

Adrenocorticotrophic hormone and adrenal steroids are being increasingly used in infectious diseases.^{89, 90} Experimentally, they appear to be of value in endotoxic shock,³⁸ but some authors^{91, 92} have not found them of value in hemorrhagic shock. Kurland and Freedberg⁹³ noted a potentiation of pressor response to norepinephrine in normotensive patients after the administration of ACTH and cortisone. A recent study⁹⁴ in humans with circulatory collapse due to severe infections and in dogs with endotoxic shock did not demonstrate adrenal secretory failure. These experiments suggested that hydrocortisone had a protective effect against lethal and tissue-damaging effects of the endotoxin as evidenced by serum glutamic oxalacetic transaminase levels. However, unphysiologic doses of hydrocortisone were used. This study was confirmed by Lillehei and MacLean.²⁹

Review of the management of septic abortion

The management of septic abortion has been a subject of violent disagreement, and it is not our purpose to review these arguments. Winter,⁹⁵ in 1927, and Taussig,⁹⁶ in 1936, have exhaustively summarized the world literature on this subject. Generally, where hemorrhage was not a problem, septic abortions were handled conservative-

ly.⁹⁷⁻¹⁰⁵ Adherents to nonoperative therapy object to interference on the basis that the infection is further spread with breaking down of the natural barrier to infection. Connective tissue reaction and exudation are the primary factors in the local barrier to infection and they occur in the uterus as elsewhere in the body. Hofbauer,¹⁰⁶ in 1926, demonstrated the defensive mechanisms of the parametrium in pregnancy. Other reasons for noninterference are the addition of a shocking procedure and the risk of uterine perforation. The addition of antibiotics to the therapeutic armamentarium has strengthened the nonoperative position. Adherents for operative management have been fewer.^{107, 108} Some recent authors^{12, 13, 15} strongly recommend prompt operative removal of the foci of infection in septic abortions and have shown that surgical intervention is safe.

There is no doubt that disruption of normal tissue barriers does occur with curettage. In the patients under discussion, the infection had already spread. Even so, antibiotics were usually effective. Studdiford and Douglas,¹² however, were impressed with the fact that in many cases of septic abortion complicated by vascular collapse a large accumulation of bacteria was present in the fetal circulation and was, therefore, in a location not readily affected by antibiotics once fetal death had occurred. The problem is, then, one of eliminating the production of endotoxin by bacteria inaccessible to antibiotic levels. Hill,¹⁰⁹ in 1936, discussing the management of postabortal gas gangrene, felt elimination of the primary focus of infection was imperative. Opinion is divided in the more recent reports on postabortal gas gangrene.¹¹⁰⁻¹¹⁴ Septic abortion complicated by vascular collapse is similar to postabortal gas gangrene in that the severity of the entity is a result of bacterial toxin. We feel that elimination of the focus of infection and necrotic tissue, as in other infected wounds, and the establishment of drainage are imperative for prevention and treatment of vascular collapse in septic abortion. The evacuation of the

uterus can be performed with a minimum of anesthesia and risk.

Management

Vascular collapse due to septicemia constitutes a major medical emergency. These unfortunate patients must be given prompt and effective therapy if they are to survive long enough to allow an attempt at treatment of the infection. The basis of treatment obviously must be directed toward combating the infection and counteracting the specific effects of the bacterial endotoxin.

The blood pressure must be supported during the delay in institution of definitive therapy by a stat intravenous injection of a vasopressor agent. An intravenous infusion with a polyethylene catheter should be begun as soon as possible. Metaraminol can be administered safely by any parenteral means. The initial dose to patients in collapse can be given in the femoral vein with the intravenous infusion being started when the peripheral veins are more accessible. Intravenously, 3 to 15 mg. increases the blood pressure in 2 minutes and reaches a maximum in 5 minutes with the pressor effect lasting 25 minutes. Subcutaneously or intramuscularly the response is slower, reaching a maximum in 30 minutes and lasting 50 to 90 minutes. In an infusion, 30 to 200 mg. per liter is well tolerated; however, a dosage increase is not apparent for 5 to 8 minutes.⁵⁸ Vagotonic effects can be abolished by atropine. Norepinephrine has been more effective at times but it necessitates administration through a long polyethylene catheter. In addition, the incidence of slough is high. It is not necessary or even desirable to elevate the blood pressure to normotensive levels. It should be maintained at a level sufficient for urinary secretion of 30 to 50 ml. per hour.

All therapy must be given intravenously due to uncertainty of absorption from other routes in vascular collapse. Shock due to bacterial endotoxin is most often due to infections with *E. coli*, *Aerobacter aerogenes* and *Proteus vulgaris* although staphylococci

and streptococci may be the causative organisms. Blood and uterine cultures with sensitivity tests should be obtained on admission prior to the institution of antibiotic therapy. Prolongation of the episode may occur, during which time information concerning the antibiotic sensitivities of the organism may be available. A combination of antibiotics, particularly the broad spectrum agents which are effective against staphylococci and gram-negative bacilli, should be administered.

Hydrocortisone and Pitocin may be started in another intravenous infusion. Pitocin may be effective in completing an abortion and is usually effective in controlling bleeding. We feel these advantages of Pitocin far outweigh the possible deleterious effect of spreading the infection.

We feel strongly that these patients, in whom abortion is not complete, should have the uterine contents evacuated within 12 hours. During this interval, medical management should be well established. It may not be uncommon, as in Cases 3 and 6, to have an initial response to therapy only to have an overwhelming intensification of the collapse occur. A review of the autopsy findings of these 2 fatal cases have led us to believe that an even more radical approach may be indicated. It was clear that these patients had so much generalized pelvic and peritoneal infection and resulting toxicity that no amount of antibiotic therapy would have been effective. It should be emphasized that histories of these patients are notoriously inaccurate and that both these patients had infections of long duration. Consequently, it may be that had these patients been subjected to laparotomy with peritoneal lavage, removal of the pelvic gen-

ital organs, and establishment of peritoneal-vaginal drainage, they may have survived. In the future, patients who have a history of criminal abortion and a prolonged febrile course with vascular collapse will probably be subjected to culdocentesis to determine the presence or absence of pus in the peritoneal cavity.

Medical consultation, in particular for prevention and management of cardiac and renal complications, should be obtained.

Urinary output must be carefully recorded with an indwelling catheter and the amount of parenteral fluid limited accordingly. Other supportive measures, such as the administration of oxygen, correction of electrolyte disturbances, replacement of blood loss, and the administration of digitalis in cardiac decompensation, are essential.

Antibiotic therapy should be prolonged, preferably for 3 weeks. Close follow-up is essential for recognition of late complications.

As a corollary, patients with known septic or suspected criminally induced abortion should be observed carefully with frequent recording of vital signs to detect early evidence of vascular collapse.

Summary

1. Six patients with vascular collapse complicating septic abortion are presented.
2. The pathologic physiology and the physiologic basis for treatment are discussed.
3. Survival of patients with this complication is dependent on early recognition and vigorous therapy.
4. A plan of treatment is suggested.

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Enterobacillary septicemia and bacterial shock in septic abortion

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THE emergence of strains of bacteria resistant to the commonly employed antibiotics, together with an increasing realization that bacterial infection has not been forever eradicated from the obstetrical wards by modern aseptic techniques and therapeutic agents, has led to a refocusing of interest and attention on the problems of infection in the parturient patient. The patterns of infectious processes have been altered by the above factors and require constant reappraisal and study in the light of changing concepts in management and treatment.

Early in 1957 four deaths from septic abortion occurred at the Los Angeles County Hospital. These were similar in their clinical course to a series of cases of "placental bacteremia" reported by Studdiford and Douglas¹⁶ in 1956. In an effort to further clarify the diagnosis and treatment of this condition this study was undertaken.

The survey includes all patients who exhibited proved enterobacillary septicemia secondary to septic abortion during a 6 month interval in this hospital. During this time there were 27 cases which could be included in the study and, of these, 6 terminated fatally. The Los Angeles County Hospital in the period of this study treated approximately 1,680 abortions of all types; all deaths related to abortion were in the

enterobacillary group, emphasizing the importance of this entity.

In the present report, 10 of the 27 patients had some degree of hypotension present during their illness; the 6 deaths were also in this group. This gives a mortality rate of 22 per cent for the entire group of 27 patients, and 60 per cent for those with hypotensive reactions. It is because of: (1) the high mortality associated with this condition; (2) the difficulties in differentiating the potentially fatal cases (those patients who might progress into shock) from a more mild form of the disease; and (3) the problems of therapy in these more critically ill patients, that this review was made.

General considerations

It has been long recognized that physiologic disturbances manifested by peripheral vascular collapse, hypotension, and shock may be produced by the blood stream invasion of certain bacteria or their products. This entity has been termed "bacterial shock." Although the condition occurs with considerable frequency and has been produced in experimental animals, it is poorly understood. The experimental syndrome has been produced by the intravenous injection of endotoxin obtained from various gram-negative organisms; among the latter are the enterobacillary group of bacteria including *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus vulgaris*. It is felt that the clinical picture in human infections is likewise due to this endotoxin in the blood

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stream, from bacteremia or a major focus of infection.

The physiologic disturbances which follow the intravenous administration of such endotoxin in animals have been reported by several investigators.^{1, 5, 8, 18} These changes include profound vasomotor collapse characterized by alternating arteriolar constriction and dilatation followed by prolonged dilatation, high fever occasionally followed by hypothermia, marked leukopenia followed by leukocytosis, metabolic acidosis due to the accumulation of lactic acid in the blood and tissues, and hemorrhagic necrosis in various organs. The clinical picture in humans is closely similar, as will be seen from the case reports.

It should be pointed out that, although the occurrence of shock is much more common following gram-negative bacteremias, it may occasionally accompany gram-positive invasions. Ezzo and Knight⁶ have suggested that the mechanism of shock in the latter instances may be due to a bacterial hypersensitivity reaction rather than to an endotoxin since endotoxins have not been shown to exist in gram-positive organisms. Although the mechanism of shock may be different, the clinical picture in the two types of infection is undifferentiated.

It is obvious that the pregnant uterus affords two conditions exceedingly favorable to the development of bacterial involvement: a readily accessible portal of entry and a culture environment of the highest order. When bacterial nutriment is supplied in the nature of necrotic material associated with abortion, conditions are highly conducive for the active and extensive growth of bacterial organisms, for their entrance into the blood stream of the host, and for the elaboration of massive amounts of endotoxin. The clinical picture of bacterial shock thus becomes not infrequently a serious and potentially fatal complication of septic abortion.

Clinical data

The 27 patients in this study of enterobacillary septicemia in septic abortion have

Table I. Vital statistics

	Mild	Severe	Average
Age	27.2	28	27.6
Gravidity	6	4	5
Parity	4.1	2.1	3.4
Abortions (previous)	1.3	1.0	1.2
Length of gestation	10.5	12.3	11.2
Admitted criminal abortion (this pregnancy)	30%	80%	51%

been divided into two groups. The first group is comprised of 17 patients with the milder form of the disease; the second group contains the more severely ill patients who developed shock during the course of the infection. The average age was 27.6 years with little difference between the two groups. The average gravidity was 5, and the number of previous abortions was 1.3 in the mild group and 1.0 in the severe group. Eighty per cent of those who entered the hospital in shock or in whom shock later developed gave a history of criminal interference, while only 30 per cent of those with the more benign condition admitted to this (Table I). Criminal induction took place, on the average, 6.1 days prior to admission, with the interval for the severely ill patients being almost twice as long as that for the mild group. Because of the small number of patients in each group this difference may or may not be significant. Studdiford and Douglas¹⁸ found in their series that only one patient was in the first trimester and most were in the middle trimester of pregnancy. In the present study, the length of gestation was determined by means of two methods: the last menstrual period and the estimated size of the uterus. (When the two methods were compared, it was apparent that there was little difference.) When totals for the two methods are averaged, it is seen the length of gestation in our series was 11.2 weeks, with those in the severely ill group being about 2 weeks further advanced in pregnancy than those in the mild group. Both, however, are much lower than the

Table II. Symptoms on admission

	Mild (17 cases)	Severe (10 cases)
Bleeding	14 (82%)	9 (90%)
Fever, chills and/or sweats	13 (77%)	9 (90%)
Pain	9 (53%)	4 (40%)
Vomiting	5 (29%)	4 (40%)

Table III. Duration of symptoms before admission (days)

	Mild (17 patients)	Severe (10 patients)
Bleeding	3.5	2.5
Fever and/or chills	1.5	1.1
Pain	1.7	1.3
Vomiting	1.5	1.5

average of 16.5 weeks in the series of Studdiford and Douglas.¹⁶

A review of the past histories of these patients showed there was no prior history of cardiac, renal, gynecologic, or other disease which appeared to have an influence on the course of the present illness.

The most common complaint on admission was bleeding, which was present in 14 of 17 of the mild group and 9 of 10 of the severe group. The next most common symptoms were chills and/or sweats; these occurred in 13 of the less seriously ill patients and 9 of the more acutely ill. Pain was more frequent in the mild, while vomiting was more frequent in the severe group (Table II). Apparently, the more critically ill patients had been sick for a shorter period of time as their symptoms generally had not been present as long before admission (Table III).

While vaginal bleeding was the most prevalent symptom, it apparently was not of a severe nature, for the hemoglobin determinations on all patients averaged 12.2 Gm. per cent. It is interesting to note that it was almost 1 Gm. higher in those of the critically ill group, probably because of hemoconcentration. The leukocyte count

was, on the average, moderately elevated, but was essentially the same in the two groups. The temperature and pulse on admission were near the same levels in both groups, although the readings were slightly higher in the group of critically ill patients.

There were noticeably greater differences in the physical findings between the two groups. Eight of 10 of those in the critical group had abdominal tenderness while this was found in only half of the mild group. Pelvic tenderness (uterine and/or adnexal) was about the same in both groups.

A finding of possible significance was that the cervix was open in 11 of 17 of those with the milder condition but in only 5 of 10 of those with more severe form (Table IV). It is felt that the uterus with its contained infected material in some patients behaves like an abscess. With no pathway of drainage (a closed cervix), sterilization of the contents with antibiotics may be exceedingly difficult. Furthermore, an abscess in other parts of the body is usually well walled off and generally has a relatively poor blood supply whereas the pregnant uterus with its augmented blood supply provides a ready avenue for the passage of bacteria and bacterial toxins into the patient's circulation. Unlike an abscess in other parts of the body, the placenta has little ability to wall off an infection. While antibiotics may sterilize the blood, it is unlikely that the uterine contents will also be sterilized. It is the bacterial toxins released from the organisms in the uterus that appear to produce the devastation culminating in shock. Those patients who exhibit little or no uterine drainage (closed cervical os) are likely in potentially graver danger than those with adequate drainage.

Table IV. Clinical findings

	Mild (17 cases)	Severe (10 cases)
Abdominal tenderness	8 (47%)	8 (80%)
Pelvic tenderness	11 (65%)	7 (70%)
Open cervix	11 (65%)	5 (50%)
Hypoactive bowel sounds	2 (12%)	5 (50%)

Another of the more significant observations was that hypoactive bowel sounds were noted in 5 of 10 of the severely ill patients as compared to only 2 of the 17 patients in the milder group (Table IV). This may suggest an early peritonitis or possibly be an early nonspecific sign indicating later clinical degeneration.

From the above data one conclusion is apparent: while there are suggestive signs in the more serious cases, there is none which can be considered pathognomonic and which will allow the clinician to separate those patients who will probably respond rapidly to therapy from those who may progress into shock. However, it is felt that the signs of a septic abortion (fever, abdominal cramps and pain, vaginal bleeding, chills and/or sweats) coupled with a history of criminal intervention, hypoactive bowel sounds, and vomiting, plus a closed cervical os, should alert the clinician to the possibility that the more severe form of the disease, i.e., bacterial shock, may be impending.

Bacteriology. Blood cultures were obtained in all cases; one, unfortunately, was lost (No. 4), and one of the other showed no growth (No. 7). Both of these are included in this series because of their similarity to the other cases and because, in both, cervical cultures grew out *E. coli*. In 5 other patients from whom both cervical and blood cultures were obtained there was agreement between the two cultures in all.

By far the most common organism found was *E. coli* (18 of 25). The next most frequent was *Ps. aeruginosa* (3), then *Pr.*

Table V. Organisms found on blood culture (25 cases*)

<i>E. coli</i>	18 (72%)
<i>Ps. aeruginosa</i>	3 (12%)
<i>Pr. vulgaris</i>	2 (8%)
Paracolon bacillus	1 (4%)
Coliform bacillus	2 (8%)

*In one case two organisms (*E. coli* and *Ps. aeruginosa*) grew out.

Table VI. Antibiotic sensitivities (per cent of those tested; 26 cultures)

	Mild (18 cultures)	Severe (8 cultures)	Total (26 cultures)
Streptomycin	18 (100%)	8 (100%)	100%
Chlor- amphenicol	18 (100%)	7 (88%)	96%
Oxytetracycline	15 (83%)	5 (63%)	77%
Tetracycline	8 (67%) (of 12—6 not tested)	5 (63%)	65%
Penicillin	5 (28%)	1 (14%) (of 7—1 not tested)	24%

vulgaris (2), and paracolon bacillus (1). In two cases the organism could be identified only as coliform bacillus (Table V).

Antibiotic sensitivity tests are routinely performed on all blood cultures. However, these being in vitro sensitivity tests, they may not necessarily reflect the drugs' true capabilities in combatting infection. All the organisms were sensitive to streptomycin; however, since this drug may be given only intramuscularly, its effectiveness in a patient in shock with relatively poor peripheral circulation is open to question. In the less severely ill patient, however, it undoubtedly is efficacious. The next most effective antibiotic appears to be chloramphenicol; all 18 of the organisms found in the group of mild patients (in one case two organisms were isolated), and 7 of 8 of those present in the more severely ill were sensitive to this. In order of decreasing effectiveness are oxytetracycline (15 of 18 in the mild and 5 of the 8 in the severe group), and tetracycline (8 of 12 in the mild and 5 of the 8 in the severe). Only 5 of the organisms found in the less severely ill and one in the more severely ill group showed sensitivity to penicillin. It appears, therefore, that since chloramphenicol may be given intravenously as well as orally and intramuscularly, it is the antibiotic of choice (Table VI).

Pathology. All 6 patients who succumbed were autopsied; all showed histologic evi-

dence of septicemia. In 4 cases pulmonary edema and congestion was severe and in the other two it was considered moderate. One of the patients with severe pulmonary congestion also had early bronchopneumonia. Another patient had microscopic evidence of acute interstitial myocarditis of septicemic origin. In 5 of the cases there was no hepatic congestion; however, all showed an increased number of circulating polymorphonuclear leukocytes in the sinusoids. In the sixth case, however, there was both gross and microscopic evidence of hepatic congestion. The kidneys of 5 of the patients showed no gross or microscopic evidence of tubular degeneration or other renal pathology; in the sixth patient there was early tubular degeneration with focal necrosis. In one case there was marked adrenal cortical hemorrhage and congestion; severe edema and congestion of the adrenals existed in another; and in a third there was moderate hemorrhage which was confined to the medulla. In the 4 cases in which brain sections were available there was cerebral edema. Two of these also had microscopic evidence of nerve cell damage.

In all 6 patients there was abundant evidence of an acute infection involving the reproductive tract. In 5 cases there was significant metritis. In one there was an acute salpingitis, and 3 patients had histologic evidence of acute oophoritis involving the corpus luteum of pregnancy. In the 2 cases in which placental tissue was found, the villi contained clumps of bacteria; however, in only one of these was there microscopic evidence of placentitis. In both of these cases, however, the decidual layers were intensely infiltrated with polymorphonuclear leukocytes which also involved the superficial layers of the myometrium. In neither case were bacteria seen outside the villi. Of the 4 patients in whom placental tissue was not present, 3 had inflammatory changes of the decidua and myometrium similar to that found in those with villi present. The pathologic findings in the placental tissue, decidua, and myometrium were similar to those noted by Studdiford

and Douglas¹⁶ and tend to confirm their concept of "placental bacteremia."

Case reports

The cases presented below are representative of the various types of patients encountered in this series. They are divided into the two groups: "mild" and "severe"; the latter group is divided into "recovery" and "death" subgroups.

Group I. Mild (no shock).

Case 1. A 29-year-old white woman, gravida vii, para iv, who had had 2 abortions, was admitted at 10 P.M. on March 1, 1957. The last menstrual period was Dec. 16, 1956. She stated that 10 days prior to admission a fall was sustained which was followed by cramps and heavy bleeding with clots. Shortly thereafter the products of conception supposedly were passed. Intermittent spotting continued until admission. The night before admission chills and sweats were noted. Intervention was denied.

Review of her previous admissions revealed that the two previous abortions were septic and were self-induced with catheters.

On admission, the patient's temperature was 105.6° F., the pulse was 100 per minute, the respirations were 16 per minute, and the blood pressure was 130/90 mm. Hg. Except for obesity and the presence of shaking chills, the general physical examination was negative. The abdomen was nontender, and no masses were palpated. On pelvic examination there was noted 10 c.c. of old blood in the vault; the cervix was tender to motion, dusky, and softened. The corpus was enlarged and boggy.

The hemoglobin concentration was 14.5 Gm. per cent, and the urine was negative. Cervical and blood cultures were done. A cervical smear showed gram-negative rods and gram-positive cocci.

The clinical impression was septic abortion, probably self-induced.

Treatment consisted of an intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 5 million units of aqueous penicillin, 0.5 Gm. chloramphenicol, and 30 units of pitocin added. Several hours later a repeat pelvic examination was performed; the cervix was found to be 1.5 cm. dilated, with the corpus anterior, 12 by 8 cm. in size, and boggy. The patient was now complaining of itching and redness of the

hands. This was interpreted as being due to mild penicillin allergy for which 50 mg. of Benadryl was given orally every 4 hours, and the penicillin was discontinued. Eight hours after admission the temperature had fallen to 97.6° F. and the pulse to 70 per minute. Four days later dilatation and curettage was done under Pentothal and nitrous oxide anesthesia with the removal of an estimated 9 grams of products of conception. The patient was discharged the next day, asymptomatic.

Group II. Severe (shock).

A. Recovery.

Case 2. A 32-year-old Indonesian, gravida v, para iii, who had had one abortion, was admitted at 10 A.M., May 26, 1957, complaining of abdominal pain, moderate bleeding with clots, and fever and chills since the preceding night. She felt that the waters had started leaking that night. The last menstrual period was Feb. 12, 1957.

Review of her previous record revealed only that there had been two previous admissions during the past month for vaginal bleeding. This condition had subsided spontaneously on both occasions.

On admission the temperature was 102.4° F., the pulse was 120 per minute, and the blood pressure was 120/80 mm. Hg. Except for the skin being hot and dry, the general physical examination was negative. The abdomen was flat, with diffuse tenderness plus rebound over its lower portion. The uterus was palpable and tender 2 to 3 fingerbreadths above the symphysis. There was also moderate left costovertebral angle tenderness. Pelvic examination revealed a cervix with multiple old lacerations, marked tenderness to motion and a dark, thick discharge from the os. The corpus was enlarged and markedly tender.

The hemoglobin concentration was 14 Gm. per cent and the leukocyte count was 25,000 per cubic millimeter. The urine was normal except for the presence of 15 to 20 leukocytes per high-power field.

Cervical smear showed gram-negative rods. The clinical impression was septic abortion with associated left pyelonephritis.

Treatment consisted of an intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 5 million units of aqueous penicillin and 1.0 Gm. of tetracycline added. The patient was also given 0.25 Gm. of chloramphenicol intramuscularly. A retention catheter was inserted for observation of the urinary output. By 10 A.M.

the next day the temperature spiked to 105° F., the pulse was 110 per minute and the blood pressure was now 100/50 mm. Hg. The hemoglobin concentration and the leukocyte count were rechecked and found to be 15 Gm. per cent and 3,800 per cubic millimeter, respectively. Because the patient did not appear to be responding to therapy, the tetracycline was discontinued and 2.0 Gm. of chloramphenicol was added to the intravenous infusion. The patient was also given 3 ampules of tetanus-gas gangrene antitoxin (1,500 units and 4,000 units per ampule, respectively). At 11:30 A.M., 10 units of Pitocin was given intramuscularly and repeated again in one hour. At 1:30 P.M. the fetus was passed. One half hour later the temperature had dropped to 100.6° F., but the blood pressure was now 70/40 mm. Hg. Fifty milligrams of phenylephrine HCl and 100 mg. of hydrocortisone were added to 1,000 c.c. of 5 per cent glucose in water and given intravenously. The blood pressure subsequently rose to 90/50 mm. Hg and the urine output continued to be adequate. On this therapy the patient gradually improved and within 2 days was afebrile; the blood pressure became normal without vasopressors. Two days later withdrawal from hydrocortisone had been completed. Four days later (9 days after admission) a curettage was performed with removal of 10 grams of necrotic tissue. The patient was subsequently discharged in 2 days. Both the blood culture and culture of the placenta grew out *E. coli*. The crown-rump length of the fetus was 11 cm.

Case 3. A 31-year-old white woman, gravida iii, para ii, who was admitted at 12:30 A.M., June 2, 1957, stated that a Lysol-water douche was taken 3 days prior to admission. Ostensibly, this was not for the purpose of inducing an abortion. That night her temperature rose to "106°." A local doctor was consulted who gave her a "penicillin shot." There had also been moderate vaginal bleeding since the time of the douche, and a single episode of vomiting had occurred the day preceding admission. The last menstrual period had been March 15, 1957.

Previous history was negative except for a cesarean section performed 4 months previously.

On admission the temperature was 103.4° F., the pulse was 120 per minute, and the blood pressure was 70/40 mm. Hg. Other findings were limited to the abdomen and pelvis. The abdomen had a recent midline suprapubic scar. Marked tenderness was present over the lower abdomen with no guarding or rigidity. Examina-

tion of the pelvis revealed blood and clots in the vagina. The cervix was soft and patulous, and the corpus was the size of a 2½ to 3 months' pregnancy.

The hemoglobin concentration was found to be 13 Gm., the leukocyte count was 5,500 per cubic millimeter, and the urine was essentially negative. Blood and cervical cultures were done and a cervical smear was read as showing no gram-positive rods.

The clinical impression was septic abortion with associated septicemic shock.

Treatment consisted of intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 5 million units of aqueous penicillin, 0.5 Gm. of tetracycline, and 1.0 Gm. of chloramphenicol added. A second liter of 5 per cent glucose in water with 0.5 Gm. of phenylephrine HCl and 50 mg. of hydrocortisone added was attached in tandem to the first.

In addition, 600,000 units of procaine penicillin G, 0.75 Gm. of dihydrostreptomycin, and 50 mg. of hydrocortisone were given intramuscularly. A retention catheter was inserted for the observation of the urinary output. On this regimen the blood pressure rose to 95/65 mm. Hg. The patient continued to respond well and within 8 hours was afebrile. For the next 3 days she continued to improve and by the fifth day the blood pressure required only occasional intramuscular injections of 10 mg. of methoxamine for maintenance at normal levels. Because the hemoglobin concentration had dropped to 7.5 Gm. per cent, 1,000 c.c. of whole blood was given. Three days later no vasopressors were being used and, after a total of 6 days in the hospital, the patient was discharged. The cervical culture showed *E. coli* and *Staphylococcus albus*. The blood culture grew out *E. coli* which was sensitive to streptomycin, chloramphenicol, oxytetracycline, and tetracycline.

The patient was readmitted 4 weeks later because of vaginal bleeding of one week's duration. Dilatation and curettage was performed the next day with the removal of 30 grams of necrotic tissue. She was discharged 2 days later.

B. Death.

Case 4. A 32-year-old Mexican woman, gravida ix, para iv, who had had 4 abortions, (2 self-induced), was admitted at 12:50 A.M., Jan. 27, 1957, stating that 5 days prior to admission a high soapsuds douche was self-administered in an attempt to induce abortion. Follow-

ing this she bled daily. The night prior to admission chills and sweats developed. The last menstrual period was Oct. 24, 1956.

The past history was negative except for the previously noted self-induced abortions.

On admission, the temperature was 104.6° F., the pulse was 88 per minute, and the blood pressure was 120/70 mm. Hg. Examination of the abdomen revealed the fundus to be 8 cm. above the symphysis. On pelvic examination, a mucoid discharge was noted to be coming from the cervical os.

The hemoglobin concentration was 11.5 Gm. per cent, the leukocyte count was 1,000 per cubic millimeter, and the urine was negative. A cervical smear and culture were done and blood for culture was drawn. The smear showed no bacteria. The clinical impression was septic abortion.

Treatment at this time consisted of intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 5 million units of penicillin and 0.5 Gm. of tetracycline added. By 8:45 A.M. (8 hours later) the temperature had dropped to 99.8° F., but the blood pressure was now 60/80 mm. Hg. Crackling râles were heard over the posterior right side of the chest. On abdominal examination, tenderness was noted over the lower abdomen, and the bowel sounds were hypoactive. Pelvic examination revealed slight vaginal bleeding, with a soft, blue, undilated cervix and a tender corpus of approximately 3 months' gestation. The adnexa were negative. The extremities were cool and clammy but no cyanosis was noted. The patient was placed in the Trendelenburg position and oxygen was administered via nasal catheter. A retention catheter was inserted for observation of the urinary output. At this time, 1,000 c.c. of 5 per cent glucose and water with 16 c.c. of L-norepinephrine (0.2 per cent) and 100 mg. of hydrocortisone added was attached in tandem to the previously running intravenous infusion. Also, 0.2 Gm. of chloramphenicol and 50 mg. of hydrocortisone were given intramuscularly. Over the next 24 hours the patient's condition continued unchanged. The urinary output had been only 175 c.c. with an intake of 1,825 c.c. The blood pressure was being maintained at 80 to 100 mm. Hg systolic, but, in order to do this without overhydrating the patient, the L-norepinephrine concentration had been increased to 80 c.c. in 1,000 c.c. of glucose in water. During the preceding 24 hours the blood

urea nitrogen had risen from 18 to 40 mg. per cent, and the CO₂ combining power had dropped from 13 to 11 mEq. per liter. The serum chlorides were now 58 mEq. per liter, the sodium 126 mEq. per liter, and the serum potassium 3.9 mEq. per liter. The leukocyte count had risen to 70,000 per cubic millimeter. By now it was apparent that there was severe metabolic acidosis as well as probable lower nephron nephrosis.

During the next 2 days the patient's condition became worse. The oliguria continued with a maximum 24 hour output of 300 c.c. Râles were present over the entire posterior portion of the chest. The blood urea nitrogen had increased to 101 mg. per cent, but, because of the use of appropriate electrolytes, the CO₂ combining power had risen to 17 mEq. per liter and there was correction of the other serum electrolytes. In spite of this improvement, 3½ days following admission the patient suddenly became lethargic, the pulse rose to 140 per minute, the blood pressure dropped to 40/0 mm. Hg, and one hour later she died.

A cervical culture grew out *E. coli* as did a culture of the products of conception.

At autopsy the pathologic diagnoses were: (1) pulmonary congestion and edema; (2) acute, early bronchopneumonia; (3) cerebral edema; (4) severe adrenal cortical hemorrhage and congestion with focal necrosis; (5) acute metritis with bacterial clumps in the villi; and (6) macerated fetus with a crown-rump length of 8 cm. The final cause of death was given as postabortal sepsis.

Case 5. A 42-year-old white woman, gravida iv, para ii, who had had one abortion, was admitted at 4 A.M., Feb. 20, 1957, complaining of rupture of the membranes 2 days prior to admission followed by moderate vaginal bleeding for the next 2 days. Fever and chills occurred the day of admission, accompanied by low abdominal cramps and a foul-smelling brownish discharge. The last menstrual period was Dec. 6, 1956.

On admission the temperature was 103.2° F., the pulse was 120 per minute, the respirations were 32 per minute, and the blood pressure was 90/60 mm. Hg. Physical examination revealed a moderately tachypneic, flushed, hot woman. Significant findings were limited to the abdomen and pelvis. The abdomen revealed no masses or tenderness, and the bowel sounds were active. Pelvic examination revealed a serous discharge

from the cervical os. Surrounding the os were several yellow vesicles. The fundus was non-tender.

The hemoglobin concentration was 12.8 Gm. per cent; the urine was normal. A blood culture was drawn. A cervical smear showed many leukocytes and epithelial cells, but no bacteria. The clinical impression was septic abortion.

Treatment at this time consisted of intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 500 mg. of tetracycline added. Pitocin (10 units) was given intramuscularly every hour for 4 injections. A retention catheter was inserted in order to follow urinary output. The blood pressure was checked hourly. Three hours later there was no obtainable blood pressure. At this time the chest was clear to auscultation, but there was now present a moderate degree of cyanosis of the lips. Oxygen was started via nasal catheter, and 1,000 c.c. of 5 per cent glucose in water with 12 c.c. of L-norepinephrine (0.2 per cent), 100 mg. of hydrocortisone, and 500 mg. of tetracycline added was attached in tandem to the other intravenous infusion. On this therapy the blood pressure rose to 100/60 mm. Hg. One hour later the patient developed acute pulmonary edema for which morphine sulfate, 10 mg., was given intramuscularly and 0.8 mg. of lanatoside C was given intravenously. A positive pressure respirator and bloodless phlebotomy with use of tourniquets rotated on 3 of the 4 extremities were also used in an effort to decrease the pulmonary edema. Chloramphenicol, 500 mg., was given intramuscularly. An electrocardiogram at this time was interpreted as showing myocardial ischemia and left ventricular strain. The patient now admitted that an abortionist had interrupted the pregnancy 4 days prior to admission. Six hours after admission the hematocrit was 44 per cent and the leukocyte count was 30,000 per cubic millimeter. Eight and one half hours after admission the blood pressure dropped to 0/0 mm. Hg. In spite of massive doses of intravenous L-norepinephrine, the shock persisted and one hour later the patient died.

The blood chemistry tests on admission, the results of which were not obtained until after the patient died, revealed a blood urea nitrogen level of 13 mg. per cent, a CO₂ combining power of 9.5 mEq. per liter, and a serum potassium level of 2.4 mEq. per liter. The entire urinary output in the 9½ hour period the patient was in the hospital was only 80 c.c. with

an estimated intake of 2,000 c.c., all of which was given intravenously. The blood culture taken on admission grew out *E. coli* sensitive only to streptomycin and chloramphenicol. At autopsy the pathologic diagnoses were: (1) pulmonary congestion and edema; (2) adrenal cortical congestion; and (3) acute metritis with bacterial clumps in the villi and an associated placentitis. The final cause of death was given as postabortal sepsis.

Case 6. A 31-year-old Negro woman, gravida viii, para iv, who had had 3 abortions, was admitted at 9 P.M., March 4, 1957, complaining of vaginal bleeding with associated cramps 2 days prior to admission and chills and sweats the day of admission. Criminal intervention was denied. The last menstrual period was Nov. 12, 1956.

The past history was noncontributory except for a radical left mastoidectomy for chronic mastoiditis performed at this hospital 2 years previously.

On admission the temperature was 104.2° F., the pulse was 112 per minute, and the blood pressure was 124/88 mm. Hg. Other than moderate obesity, physical findings were limited to the abdomen and pelvis. Examination of the abdomen revealed diffuse low abdominal tenderness, questionable bilateral costovertebral angle tenderness, and active bowel sounds. On pelvic examination the cervix was noted to be pink and firm with a closed os. Surrounding the os was a small area of erosion. The fundus was enlarged.

The hemoglobin concentration was 12 Gm. per cent and the leukocyte count was 8,400 per cubic millimeter. The urine revealed 2-plus albumin and 6 to 8 leukocytes per high-power field. The clinical impression was threatened abortion with an associated pyelonephritis.

Treatment consisted of 200 mg. of tetracycline intramuscularly plus 250 mg. orally every 6 hours; phenobarbital, 30 mg. 4 times daily; absolute bed rest; and a temperature check every 2 hours. After an initial drop of the temperature to 101° F., 10 hours after admission it rose to 104° F. The patient's condition was re-evaluated, and pelvic examination revealed a soft, blue, closed cervix from which a bloody discharge was emerging. The corpus was soft and tender and was estimated to be 10 by 6 cm. The adnexa were moderately tender, but no masses were noted. The diagnosis was now changed to septic abortion. A blood culture was drawn; a cervical smear showed gram-negative rods and gram-positive cocci, some in

chains. Repeat leukocyte count revealed a drop to 3,400 per cubic millimeter. Treatment was changed to 200 mg. of chloramphenicol intramuscularly every 6 hours. A retention catheter was inserted for observation of the urinary output, and the blood pressure was checked every half hour. During the next 12 hours, the patient's condition was essentially unchanged, but the blood pressure dropped as low as 90/60 mm. Hg on occasion. The next morning (38 hours after admission), the temperature rose to 105° F. and the pulse to 160 per minute; the blood pressure had again fallen to 90/74 mm. Hg. Two hours later the patient was in obvious shock with a blood pressure of 72/56 mm. Hg. The temperature dropped to 100° F., and the pulse to 112 per minute. Significantly, she had been essentially anuric over the past 16 hours with a urinary output of only 105 c.c. Three hours later dilatation and curettage was performed, and an estimated 20 grams of necrotic tissue was removed. Anesthesia was nitrous oxide and Pentothal. Following operation the patient appeared to improve; the blood pressure became easier to maintain and the urinary output increased to 300 c.c. during the first 3 hours following operation. By this time the patient had been taken off of all intramuscular and oral medication and was receiving an intravenous infusion of 1,000 c.c. of glucose in water with 150 mg. of hydrocortisone and 1.0 Gm. of chloramphenicol added. Via a tandem attachment a second 1,000 c.c. of glucose in water with 40 c.c. of L-norepinephrine (0.2 per cent) was added. The patient by now had developed marked metabolic acidosis with a CO₂ combining power of 13 mEq. per liter. The blood urea nitrogen level was 33 mg. per cent. The acidosis was being corrected by intravenous infusion of the appropriate electrolyte solutions. The next day, 20 hours after the development of shock, the temperature rose to 105° F., the pulse to 160 per minute, and the respirations to 60 per minute. Two hours later complete vasomotor collapse developed, a generalized seizure occurred, and the patient died. One of the attendants subsequently obtained the history that 4 days prior to admission an abortion had been attempted with a high soapsuds douche.

The blood culture grew out *Pr. vulgaris*, sensitive only to streptomycin and chloramphenicol.

At autopsy the pathologic diagnoses were: (1) pulmonary congestion and edema; (2) acute myocarditis consistent with septicemic origin; (3)

cerebral edema; (4) postabortal uterus with minimal metritis; and (5) acute oophoritis involving the corpus luteum of pregnancy. The final cause of death was given as acute myocarditis secondary to septic abortion.

Case 7. A 20-year-old Mexican woman, gravida i, para 0, was admitted to the Communicable Disease Unit of this hospital at 12 noon, May 9, 1957, because of a possible meningococcic meningitis. She stated that 3 days prior to admission her period started. By the next day this had become a profuse pink discharge. The day before admission nausea and vomiting developed with associated chills and diarrhea, and that night a rash appeared on the face and trunk. The last menstrual period was in March, 1957.

On admission the temperature was 97° F., the pulse was 108 per minute and the blood pressure was 60/40 mm. Hg. The general physical examination was negative except for a petechial rash over the trunk and arms. On examination of the abdomen, the uterine fundus was palpated 4 cm. above the symphysis, there was no tenderness, and the bowel sounds were normal. Pelvic examination revealed a presumably pregnant uterus with a dilated cervix.

The hemoglobin concentration was 14 Gm. per cent; the leukocyte count was 35,000 per cubic millimeter. On lumbar puncture the spinal fluid pressure was 150 mm. of water; the Pandy test for protein was negative, and there were 15 cells per cubic millimeter. No organisms were seen on direct smear of the petechiae.

The clinical impression was meningococcemia with associated threatened abortion. The shock was assumed to be secondary to the meningococcemia.

Therapy consisted of intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 5 million units of aqueous penicillin, 50 mg. of hydrocortisone and 50 c.c. of a highly purified extract of whole adrenal cortex (Eschatin). In addition, the patient was given 1 million units of penicillin as a direct intravenous injection; 3.0 Gm. of combined sulfamerazine and sulfadiazine was given subcutaneously, and 10 mg. of methoxamine was given intramuscularly. The hypotension did not respond either to the latter or to intravenous infusion of 150 mg. of phenylephrine HCl in 1,000 c.c. of glucose in water; therefore, 4 c.c. of L-norepinephrine (0.2 per cent) added to 1,000 c.c. of 5 per cent glucose in water was started intravenously. The blood

pressure shortly rose to 110/80 mm. Hg. Within 2 hours the concentration of L-norepinephrine had to be increased to 36 c.c. per liter of fluid.

Six hours after admission the patient was seen by the gynecologic consultant. At this time she admitted that a friend had induced an abortion with a catheter one week prior to admission. The fetus had been passed 2 days prior to admission. Abdominal examination by the consultant revealed a soft, nontender suprapubic mass consistent with a 2½ to 3 months' pregnancy. On pelvic examination the cervix was soft, blue, and dilated 3 cm., with placental tissue palpated in the os. The corpus was soft, globular, and 10 by 12 cm. in size.

The patient was skin-tested for tetanus and gas-gangrene antitoxin and was given 60,000 units of the gangrene antitoxin subcutaneously. A blood culture was drawn and cervical smear and culture were done. No gram-positive bacilli were seen in the cervical smear. Urinalysis was negative except for the presence of many gram-negative bacilli.

The sulfonamides and Eschatin were discontinued, and an intravenous infusion of 1,000 c.c. of 5 per cent glucose in water started, with 500 mg. of phenylephrine HCl, 1.0 Gm. of chloramphenicol and 200 mg. of hydrocortisone added. An additional 1.0 Gm. of chloramphenicol was given intramuscularly. Twelve and one half hours after admission the patient went into profound shock with no obtainable blood pressure. One and one half hours later she died. The total urinary output for the 14 hours was 100 c.c.

The cervical culture grew out *E. coli*, but the blood culture showed no growth, possibly as a result of its being drawn after antibiotic therapy had been started.

At autopsy the pathologic diagnoses were (1) pulmonary congestion and edema; (2) cerebral edema with acute nerve cell changes; (3) adrenal cortical congestion; (4) postabortal uterus with acute metritis; and (5) acute oophoritis involving the corpus luteum of pregnancy. The final cause of death was given as postabortal sepsis, *E. coli*.

Comment

The preceding cases emphasize the urgent importance of early recognition and prompt treatment of bacterial shock in septic abortion. It is obvious that, as mentioned previously, there are no pathognomonic signs

or symptoms which will readily separate such patients from ones who will respond rapidly to simple therapy. However, those findings which should alert the clinician, given obvious evidence of a septic process, are: (1) suspicion of criminal abortion; (2) the presence of hypoactive bowel sounds (especially if there is associated vomiting); and (3) a closed cervical os.

Equally important is the close observation of *all* cases of septic abortion. Such observation should include frequent checking of the vital signs, especially the blood pressure. There is almost always adequate warning of developing hypotension; shock in these cases rarely appears without a prodromal period of gradually falling blood pressure.

In the severe cases of septic abortion, a retention catheter should be inserted for recording the urinary output. The latter should be calculated at least every 8 hours, and some cases may require an even closer check if renal failure appears to be developing. The urinary output should be kept, if possible, above 40 c.c. per hour (900 c.c. per day). Moreover, since patients in early renal failure may not exhibit oliguria but only the tendency to a fixed specific gravity (1.010), the latter should also be checked regularly. The appearance of proteinuria also should alert the physician that renal damage may be occurring.

Serial hematocrit counts should be taken, if indicated, in order that developing hemoconcentration may be recognized. Such may represent inadequate fluid intake, or a shift of fluids from the intravascular to the extravascular compartments due to developing vascular incompetence (impending septic shock).

Both cervical and blood cultures, plus a cervical smear and Gram stain, should be performed. Not infrequently the gram-negative bacilli will be seen on direct smear. The cultures are merely confirmatory.

The present study indicates that the best antibiotic therapy rests with streptomycin and chloramphenicol. Streptomycin is given intramuscularly, 2 to 4 Gm. daily, in divided

dosage. Since its only route of excretion is via the kidneys, streptomycin should be used cautiously when renal output is impaired because of the danger of toxic levels accumulating.⁹ Chloramphenicol is given as an intravenous infusion, 0.5 to 2.0 Gm. per liter of infusant. Intravenous administration is to be preferred to the oral or intramuscular route because of the more rapid, higher, and more constant blood levels obtainable. Also, if shock is present, absorption of the antibiotic from the gastrointestinal tract or an intramuscular site may be poor.

The use of hydrocortisone is also advocated, as it is felt that septicemic shock may be due in part to a relative degree of adrenocortical failure. The latter may be the result of hemorrhagic necrosis of the adrenals, septic adrenal involvement, and the postulated chronic stress of pregnancy with resultant inability to adapt to superimposed stressful insults.¹² The fulminant cases often resemble the Waterhouse-Friedrichsen syndrome in their course.

It should also be pointed out that derangements of the acid-base balance are a frequent and serious complication of enterobacillary septic abortion and should be watched for closely. In the series of cases herein reported, this disturbance invariably took the form of metabolic acidosis (Cases 4, 5, and 6).

These patients frequently run high temperatures which in turn cause profuse sweats. During heavy sweating, large quantities of base in the form of sodium and potassium will be lost. As much as 75 mEq. of sodium may be excreted per liter of perspiration.² Large amounts of sodium, chloride, and potassium are also present in vomitus. In 3 liters of vomitus (gastric) approximately 50 mEq. of potassium alone may be lost.² It has been noted previously that vomiting occurred in 40 per cent of the severely ill patients.

As mentioned earlier in this report, it has been demonstrated that the administration of the endotoxins of various gram-negative organisms will produce, in exper-

imental animals, accumulation of lactic acid, which in turn causes metabolic acidosis. It is probable the same changes occur in humans. Hence, in enterobacillary septic abortion there are at least three major mechanisms for the development of metabolic acidosis: (1) excessive sweating, (2) vomiting, and (3) septicemia.

It is felt that, provided urinary output is adequate, electrolyte solutions, such as physiologic saline with added potassium or Ringer's solution, should be given to prevent the development of acidosis. If metabolic acidosis is present, intravenous solutions, such as sodium lactate with added potassium or Ringer's lactate, should be administered.

It is obvious that, in addition to replacing electrolyte loss, it is also necessary to replace water loss. In those patients who are not vomiting supplementary replacement via the oral route may be attempted with substances high in sodium and potassium (i.e., beef broth, orange juice).

Many investigators^{4, 7, 14, 16} feel that early surgical intervention is of major importance in the treatment of those patients who do not appear to be responding to the usual therapy. O'Donnell,¹¹ in a discussion of postabortal oliguria, indicates that in septic abortion there may be toxic substances liberated from the retained dead and dying placental tissue, and these may be absorbed by that circulation present in the still viable portions of the placenta. These substances, coupled with bacterial toxins, may act synergistically to damage renal tubules, causing lower nephron nephrosis and/or the more generalized damage noted in these patients (shock, cerebral edema, and pulmonary congestion and edema). Based on this concept, O'Donnell¹¹ also advocated early evacuation of the uterus in these patients. Recent publications by Tenney and associates¹⁷ and by Brown and Hanisch⁸ have pointed out the values of a more aggressive approach in the management of septic abortion.

In this series, a surgical procedure (dilatation and curettage) was utilized in only

2 patients while they were still critically ill. One died within one hour and the other approximately 22 hours following operation (Case 6). In spite of our poor success with operative management we still feel it is of value. In cases where it has become apparent that the patient is not responding to therapy, as evidenced by the continuance of fever and gradually falling blood pressure, surgical intervention in the form of either sponge-stick evacuation or dilatation and curettage, depending upon the situation, should be seriously considered. It is only in this manner that progressive septicemia may be abated if there is a mass of necrotic tissue serving as a nidus of infection. Tenney and co-workers¹⁷ have advocated curettage within 12 hours of hospitalization or antibiotic therapy. In severe cases, evacuation of the uterus may be lifesaving.

The treatment of hypotension of the type herein discussed demands immediate resort to the antihypotensive agents:

Vasoxyl—methoxamine HCl (10 to 50 mg.; 20 mg. per cubic centimeter)

Neo-synephrine—phenylephrine HCl (50 to 500 mg.; 10 mg. per cubic centimeter)

Levophed—L-norepinephrine (levarterenol bitartrate) (4 to 40 c.c.; 0.2 per cent solution)

In our hands, phenylephrine HCl as an intravenous infusion has been effective in treating early shock and milder cases. Patients with more severe involvement usually require L-norepinephrine to sustain blood pressure at reasonable levels. By experience, we have come to resort to norepinephrine only when other vasopressors are ineffective. There appears to be greater difficulty in "weaning" the patient off this drug, as regards blood pressure maintenance, than occurs with other antihypotensive agents. Although any hypovolemia must be corrected, the hypotension of septic shock is out of proportion to the blood loss, and blood transfusion alone does not usually improve the condition.

Although in this series there was only one case which could be classified as acute tubular necrosis, the relatively high inci-

dence of this condition in septic abortion reported in the literature^{10, 11, 13, 15} makes it mandatory that the likelihood of its occurrence in any septic abortion be constantly appreciated. When it does occur, fluids should be restricted and electrolyte balance carefully maintained during the oliguric phase. Replacement of insensible and other fluid loss may be achieved with intravenous 10 per cent glucose in water. Higher concentrations of glucose may be used so as to provide calories for metabolism, thus reducing endogenous protein catabolism. Electrolyte therapy should be controlled by frequent serum electrolyte determinations (carbon dioxide combining power, sodium, chloride, urea nitrogen, potassium). Daily electrocardiograms should be obtained as an adjunctive aid in evaluating serum potassium levels.¹⁵

Finally, since anemia may occur in these patients, adequate blood replacement should be utilized as necessary. If urine output is adequate, this offers no greater problems than those encountered treating any anemic patient with transfusions. However, it should be remembered that pulmonary edema and/or congestion was present in all of our fatal cases, none of which was treated by transfusion. Hence, septic abortion may increase susceptibility to the development of pulmonary edema following blood transfusion. If lower nephron nephrosis has developed, or if there is reasonable possibility of its onset (decreasing renal output), whole blood should not be used for transfusion

because of its higher potassium and protein (plasma) content. To be preferred is the use of suspensions of washed, packed erythrocytes.¹⁵

Summary

A series of 27 cases of enterobacillary septicemia in septic abortion seen at the Los Angeles County Hospital during a 6 months' period has been reviewed. In this group of patients the mortality rate was 22 per cent.

Ten of the 27 patients suffered from the hypotension of bacterial or septicemic shock. All 6 deaths in the total series were in this group.

The symptomatology and physical findings have been discussed as regards their possible significance in the treatment and prognosis of septic abortion. Autopsy and bacteriologic findings have also been correlated.

Seven case reports illustrating the various problems that may occur are included.

Therapy has been discussed, with emphasis on the early detection and management of hypotension and peripheral vascular collapse (septicemic shock). The role of early uterine evacuation is considered.

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The x-ray diagnosis of gas gangrene of the uterus

Report of a case

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ALTHOUGH *Clostridium welchii* infections of the uterus are not commonly encountered in the private practice of obstetrics and gynecology, their occurrence in the clinic population of a large hospital is not unusual. Hill¹ reported the incidence of post-abortal sepsis caused by this organism to be one per cent in his experience. Our incidence at this institution does not approach that figure, but the disease does occur often enough to make us suspect the diagnosis in septic abortions.

All authorities agree that early diagnosis is imperative if the course of the infection is to be altered. The radiologic diagnosis of clostridium infections has been referred to in the literature, but it is our impression that radiography is not commonly used as a diagnostic tool. In 1941 Poppel and Silverman² published the only films that we were able to find in the literature demonstrating gas within the wall of the uterus. In a recent case at this hospital a radiologic diagnosis of gas gangrene was made before the condition was suspected clinically, but which was later confirmed bacteriologically. The films aptly demonstrated the disease, but

since the obstetric and gynecologic literature does not include this x-ray demonstration, a case report with the films was considered of interest.

Mrs. R. R., a 29-year-old Puerto Rican gravida vi, para iv, who had had one abortion, was admitted to the gynecologic service of this hospital on the evening of Jan. 5, 1958, complaining of crampy abdominal pain and vaginal bleeding of 12 hours' duration. The patient's last menstrual period was Nov. 12, 1957, and she stated that she had been symptom-free until the night of admission when she fell off a chair. The following morning the patient noted the pain followed by the bleeding. She vehemently denied operative interference at any time. Physical examination on admission revealed a well-developed, rather pale, moderately dehydrated woman in no acute distress. Blood pressure was 90/60, temperature 101.4° F., pulse 100. Other positive findings were limited to the abdomen and pelvis. A tender suprapubic mass was noted just above the symphysis with minimal deep lower abdominal tenderness without rebound. Bimanual examination revealed a slightly tender uterus the size of an 8 to 10 weeks' gestation, a 3 cm. dilated cervix with tissue presenting at the os. The tissue was removed, and the patient was treated with bed rest and intravenous fluids.

The next day her condition had markedly deteriorated, and signs of a spreading pelvic peritonitis were present. The uterus was exquisitely tender, and a foul discharge was noted from the endocervical canal which was gram stained and cultured for aerobic and anaerobic

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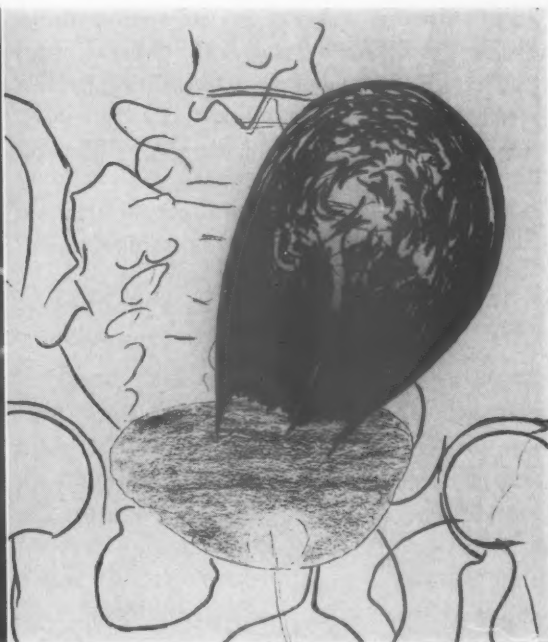
organisms. The urinary output had been only 75 ml. since admission, and cystograms were performed to rule out traumatic perforation of the bladder secondary to the suspected induced abortion (Figs. 1 and 2). X-ray examination revealed an abnormal gas shadow in the lesser and greater pelvis. The gas was arranged in an onion-peel fashion within a mass which probably represented the uterus. A diagnosis of an aerogenic infection of the uterus was made, most likely due to a clostridial organism. An infection with the colibacillus was considered remotely in the differential diagnosis. Gram stain was reported as equivocal for the presence of gram-positive spore-forming rods.

She was placed on massive doses of aqueous penicillin and intravenous tetracycline with close observation of the intake and output. Her intake was regulated to equal 500 ml. plus her output. Cultures were reported as strongly positive for *Cl. welchii* and *coli-aerogenes*. Repeated blood cultures were negative, and there was never any evidence of intravascular hemolysis.

In the next few days the output gradually increased and the patient's general condition improved slightly. Daily electrolytes and electrocardiograms for evidence of hyperkalemia were

carefully watched. A metabolic acidosis was treated with small amounts of sodium lactate. On the fourth day after admission the patient was afebrile, and on the fifth day cultures were negative for *Cl. welchii*. On the eighth day of therapy the urinary output had increased to 750 ml., but a fixed low specific gravity of the urine was present. In spite of the increasing output and control of the electrolytes, her condition again began to deteriorate. On the tenth day following admission the patient became apathetic and lethargic and she responded poorly to the spoken word. For the first time the electrocardiogram showed evidence of hyperkalemia, and the serum potassium jumped from a previous high of 4.8 mg. per 100 c.c. to 5.7 mg. The blood urea nitrogen rose from 89 mg. per 100 c.c. to 112 mg., and the blood pH dropped to 7.26. At this time she was transferred to another institution for dialysis on the artificial kidney, which was carried out shortly after admission there.

After dialysis, the electrolytes and pH approached normal, but her general condition failed to improve. The daily output ranged between 240 and 270 ml. of urine, and the potassium levels again began to climb. Her clinical



Figs. 1 and 2. A cystogram performed for exclusion of an injury to the urinary bladder revealed gas in an atypical arrangement. The gas formed onion peel-like layers. The arrangement of the layers conformed to the muscular layers of a moderately enlarged uterus. A semischematic sketch amplifies the radiographic findings.

course continued to degenerate, and the patient died on the sixth day after dialysis. Post-mortem examination revealed a severe endometritis and myometritis without evidence of perforation, and acute tubular degeneration of the kidneys.

Comment

Although the outcome in this case was unfavorable, the diagnosis was made by x-ray examination relatively early in the course of the infection. We are in entire agreement with de Alvarez and Wolter³ that routine gram stains with aerobic and anaerobic cultures of the endocervical canal are requisites for early diagnosis, but in addition we believe that x-ray examination of the lower abdomen and pelvis should be routine in all cases of septic abortion. The benefits of this simple diagnostic procedure are threefold: (1) gas gangrene of the uterus, although not common, may be diagnosed on admission before cultures can be reported and when gram stains are equivocal; (2) foreign bodies left in situ in the uterus or abdomen following criminal abortion may be seen; (3) direct or indirect evidence of peritonitis may be evident.

The place of surgery in the management of this condition is not well defined, but, since results have not been encouraging, the conservative approach is usually followed. The place of polyvalent antitoxin in therapy

is also debatable. With the dosages of antitoxin required, this modality of treatment is not entirely innocuous and yields mixed results, although it is frequently employed. With more precise understanding of acute renal failure and fluid and electrolyte balance and the practical application of the artificial kidney, coupled with early diagnosis, the salvage rate should be higher in a heretofore uniformly fatal condition.

Summary

1. A detailed case report of a *Clostridium welchii* infection of the uterus is presented with evidence of the disease demonstrated by x-ray examination.

2. Radiography of the abdomen and pelvis is urged as a diagnostic procedure, combined with smears and cultures, in an effort to make the early diagnosis of gas gangrene of the uterus.

We are deeply indebted to Miss Ann White, the hospital librarian, for her editorial assistance in the preparation of this paper.

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Cervical incompetence: current therapy

WAYNE F. BADEN, M.D.*

E. E. BADEN, M.D.

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THE purpose of this paper is threefold. First, we wish to present a series of cases of cervical incompetence begun as a single case report¹ in 1957. The second purpose is to introduce "bridge" tracheloplasty as a simple, promising, external os surgical therapeutic procedure. Last is the desire to establish the relative indications for "bridge" tracheloplasty and for other procedures preliminary to presentation of a program for management of these unfortunate women.

Over two dozen papers published in the past 3 years attest the importance of this entity. Present interest centers primarily upon *when* and *how* to treat it. Its reported incidence varies from 1:300¹ to 1:540² pregnancies. Multiple etiological factors are frequently found and no consistent causes have been established.

Cervical incompetence is any condition of the uterine cervix that permits sufficient "painless" dilatation to allow spontaneous rupture of the membranes and subsequent onset of labor *prior to the end of the thirty-sixth week of gestation*. Occasionally, dilatation is sufficient to initiate labor before the membranes rupture. The history alone is strong evidence of the disorder. Successive pregnancies may cause earlier and earlier

labor as the cervix weakens with each assault. Warning signs of impending danger may be low abdominal "pressure," "irritable" uterus, expulsion of the mucous plug, "watery" discharge from developing amnionitis, and "bloody" show. Irreversible labor and fetal loss may rapidly follow. Numerous authors have adequately discussed the adjunctive diagnostic measures, including use of the No. 6 Hegar uterine sound,¹¹ hystero-grams,^{3, 4, 5, 12} and postabortal cervical palpation.⁷ Because apparently normal cervixes become incompetent and because apparently abnormal cervixes often maintain a pregnancy, the authors place but modest stress upon these procedures. The only absolute proof of cervical incompetence is the actual palpation and visualization of the dilating cervix *during* pregnancy. Progressive cervical dilatation to *over* 1.5 cm. with effacement of *over* 50 per cent or with severe old cervical lacerations warrants the diagnosis of incompetence.

Pregnancy care—tracheloplasty techniques

Nonsurgical management of all suspected cases calls for weekly vaginal examinations after 12 weeks of gestation. After the sixteenth week a well-fitting abdominal support is worn when the patient is ambulatory. Moderate daytime rest and sleep at night on a bed elevated 6 inches at the foot in slight Trendelenburg position is advised. Medications* are given upon individual indications.

*Releasin, Lutrexin, progesterone, thyroid, Pamine Br, Sparine, Hesper-C, and sedatives were special medications given on clinical indications and with equivocal results.

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If vaginal examination reveals true incompetence, the patient is hospitalized at bed rest with the foot of the bed elevated, while the cervix recuperates and the membranes recede. Labor must be ruled out by a 12 to 24 hour observation period. A Furacin vaginal suppository is gently inserted and a broad-range antibiotic begun. Operation is done under mild analgesia and light Pentothal anesthesia. The cervix is handled with ring forceps and Russian thumb forceps. Scissors are used to denude the 1 cm. wide strip of exocervix. Anatomic repair of old cervical lacerations may be incorporated into the procedure. Interrupted vertical mattress sutures of chromic No. 0 catgut, placed at 1 cm. intervals, approximate the denuded anterior and posterior cervical lips.

The original procedure, described in previous publication¹ and shown in Fig. 1, *a-c*, denudes the exocervix *laterally*. When these raw areas are sutured anteroposteriorly, there remains a small, central external os less than 0.5 cm. in diameter. "Bridge" tracheloplasty, the newer and more satisfactory procedure now introduced, reverses the first technique in that the denuded area is *central*, as shown in Fig. 1, *A-C*. Thus, when these denuded areas are sutured anteroposteriorly, the result is 2 lateral ora, both leading to the endocervical canal. This extremely simple procedure forms an efficient "bridge" under the membranes, preventing their rupture and inhibiting cervical dilatation. A small plastic tube drain (1 to 2 mm. in diameter) may be placed in one new exter-

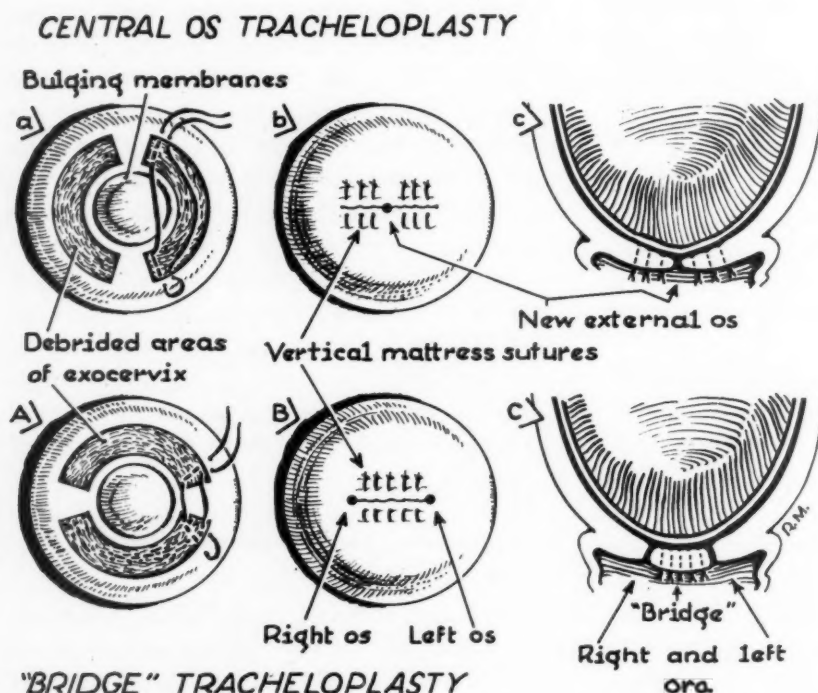


Fig. 1. *a-c*, Central os tracheloplasty (the original technique). *a*, View of dilated exocervix, showing 2 lateral débrided areas 1 cm. wide, and one vertical mattress suture of chromic No. 1 catgut in place. Note the bulging membranes centrally. *b*, Lateral débrided areas sutured anteroposteriorly. Note single, central external os, now approximately 0.5 cm. in diameter. *c*, Transverse section of the cervix through the new external os, showing the additional support for the membranes. *A-C*, "Bridge" tracheloplasty (the preferred technique). *A*, View of the dilated exocervix, showing anterior and posterior débrided areas 1 cm. wide and one vertical mattress suture in place. Membranes are again shown bulging centrally. *B*, Débrided areas sutured anteroposteriorly. Note the 2 lateral ora. *C*, Transverse section of the cervix through the 2 new ora, showing the central "bridge" supporting the membranes and inhibiting dilatation of the cervix.

nal os and out the other, prior to closure of the "bridge." This is removed in 4 or 5 days.

Postoperatively, the patient with minimal preoperative cervical dilatation is allowed cautious ambulation beginning the second day, later in the more severe cases. Antibiotics and other medications are continued as indicated. Mild laxatives prevent straining. The patient wears an abdominal support and sleeps in the Trendelenburg bed until labor. Weekly vaginal examinations are done at home or in the office and ambulation increased according to the status of the cervical scar. Some patients are up only for bath and meals, while others become completely ambulatory. If labor occurs immediately postoperatively, the sutures are cut and delivery allowed. If labor occurs later, the "bridge" is cut under direct vision, when possible, although blind "digital" lysis was done once without difficulty. These patients must be carefully watched and, if labor begins, lysis of the "bridge" must be promptly carried out. The "bridge" is usually quite thin at term and induction of labor may be performed at the time of lysis. Lysis commonly allows several centimeters of cervical dilatation and a short labor is expected. Pressure from the descending fetal head has stopped any excessive cervical bleeding. Following delivery any old or new cervical laceration should be repaired.

Material and results

Of the 10 completed surgical and non-surgical cases, a successful conclusion was reached in 7 (70 per cent). Two were nonsurgically treated patients with 100 per cent success, while the other 8 required operation with 63 per cent success. The patients' ages ranged from 25 to 39, averaging 34. These patients had only 14 (27 per cent) living infants from a total of 52 pregnancies. Cervical incompetence, specifically, had lost each patient an average of nearly 3 babies with the maximum of 11 in one patient. Previous difficulty in conception had been noted in 2 (20 per cent). The typical history of premature spontaneously ruptured membranes followed by labor was found in

9 (90 per cent). Prior cervical trauma was probable in at least 6 (60 per cent). In 2 of our cases, a No. 4 Hegar uterine sound was passed with difficulty both *before* and *after* the respective pregnancies. Hystero-grams were essentially normal in one of these patients. True cervical incompetence was unequivocally confirmed by vaginal examinations during pregnancy in all patients.

One of the 2 nonsurgical patients was handled by Dr. H. C. McGrede, Jr., of Longview, Texas. Vaginal examinations, weekly or oftener, abdominal support, Trendelenburg bed, and medication based on individual indication served as nonsurgical measures. The first patient, a para 4-4-0-3 with 4 consecutive fetal losses, was advised to have the operation when 2 cm. of cervical dilatation developed at 28 weeks' gestation. The surgical procedure was refused and she was delivered of a surviving infant 3 weeks later, having maintained the pregnancy 4 weeks longer than usual. The second patient, a para 0-2-1-0 with all three losses due to incompetence, delivered a healthy infant at 34 weeks' gestation, having prolonged the pregnancy about 12 weeks longer than usual. Average weight was 1,925 grams for each infant.

Four of the 8 surgical cases were from the Raymondville Memorial Hospital, Raymondville, Texas. Dr. H. C. Henderson, Jr., and Dr. James E. Gleichert operated upon one patient each at the Dallas Methodist Hospital in Dallas, Texas. Two patients were operated upon by Dr. H. C. McGrede, Jr., at the Longview General Hospital in Longview, Texas. Operation was performed from the fourteen to the thirtieth week of gestation, averaging the twenty-third week. The pregnancies then continued from one day to 23 weeks following the surgical procedure, averaging 9 additional weeks. The average patient was delivered at 32 weeks' gestation with the successful cases averaging over 36 weeks and the failures only 26 weeks of total gestation. However, even these failures were prolonged an average of 6 weeks each. Central os tracheloplasty sustained pregnancy for an average of 8 weeks with 2 (67 per

cent) of 3 infants surviving. "Bridge" tracheloplasty maintained pregnancy for an average of 11 weeks with 3 (60 per cent) pregnancies being successfully completed. Longer preoperative observation would have contraindicated the operative procedure because of labor in 2 failures and might have improved the relative success rate to 83 per cent. Birth weights averaged 2,004 grams for the surgical cases. Babies in successful cases averaged 3,047 grams and in failures only 936 grams each. All deliveries were vaginal.

Comment

Gradation of incompetence. The severity of this disorder bears directly upon the expected fetal survival. Cervical lacerations and effacement must be considered in evaluating the incompetence in a given patient, but most critical is the amount of cervical dilatation necessary to make the diagnosis. Dilatation of *over* 1.5 cm., especially if accompanied by *over* 50 per cent effacement or severe cervical lacerations, serves to establish the diagnosis in pregnancy. After the thirty-sixth week of gestation the entity is of little clinical importance since a mature infant is then anticipated. The duration of gestation when the above amount of cervical dilatation occurs gives us basis for grading the degree of incompetence in any patient.

We would like to suggest the following gradation of cervical incompetence: Grade I, the mildest form, would include those cases occurring from the thirtieth through the thirty-sixth week; Grade II from the twenty-fourth through the thirtieth week; Grade III from the eighteenth through the twenty-fourth week of gestation; and Grade IV all those earlier than this. Our surgical series revealed no Grade I cases operated; 4 Grade II cases were operated with 100 per cent success; 3 Grade III cases were operated with no survivals; and one Grade IV case was operated with survival. Our 2 non-surgically handled cases, previously Grade II and Grade IV, respectively, both became Grade I patients with surviving infants upon wearing abdominal supports and using Trendelenburg beds. Obviously, even Grade IV

cases are not hopeless, although the prognosis improves in the milder grades.

Therapy. Surgical therapy should be restricted to those patients not responding to the various indicated medications, the use of a well-fitting abdominal support, and elevation of the foot of the bed for modest daytime rest and sleep at night. It is also indicated in nonpregnant patients with strongly positive histories of 2 or more fetal losses from cervical incompetence.

Surgically, the cervix has been attacked at the internal,^{2, 13} mid-cervical,⁸ and external os levels,¹ as well as all 3 simultaneously.¹² Shirodkar's¹³ internal os circlage technique and his modifications^{2, 9} have received the most attention and report approximately 70 to 85 per cent success. McDonald⁸ has had 40 to 50 per cent success with his mid-cervical, intravaginal circlage suture. Our own initial success with external os tracheloplasty is 63 per cent. Lash⁶ reports 61 per cent over-all success following repair of the entire length of the cervix, as indicated. Of all techniques, the simplest to perform are McDonald's and external os tracheloplasty. No ideal material for encircling the internal os that will assure cervical competence, yet allow vaginal delivery, has been reported.

When to operate is as important as operative technique. In the nonpregnant state one may choose the Lash¹² or Shirodkar¹³ (or most modifications thereof^{2, 9}) procedures. The Shirodkar technique may also be used during pregnancy. McDonald's⁸ operation is confined to pregnancy, as is external os tracheloplasty.

The proper procedure may be further determined by consideration of the necessary postoperative care. Shirodkar, Lash, and McDonald allow ambulation. External os tracheloplasty allows ambulation in varied degrees. The Shirodkar and Lash techniques usually necessitate secondary cesarean section at delivery, while McDonald and ourselves allow vaginal delivery. For delivery in later pregnancies, Shirodkar and Lash perform repeat cesarean sections without the necessity of repeating the original cervical pro-

cedure. Page⁹ uses Oxygel in the internal os area for scarring effect with 70 per cent success in his 10 reported cases. Delivery was vaginal. He¹⁰ also mentions the danger of a ruptured uterus as a complication of internal os procedures when nonabsorbable circlage materials are used.

Suggested regimen for therapy

In view of the 20 per cent success with nonsurgical management, we feel that "suspected" cases should be handled in that manner until actual cervical incompetence is observed by weekly vaginal examinations during pregnancy. Cases proved during pregnancy and nonpregnant women with a positive history of at least 2 fetal losses from cervical incompetence deserve operation. This latter group of patients will best be served by Shirodkar's¹³ or Page's⁹ internal os procedures. If cervical lacerations are extensive, however, then a thorough Lash¹² operation must seriously be considered. In spite of 2 failures with the Lash procedure, we feel that postabortal cervical palpation and repair, as recommended,¹² is worthy of trial. During pregnancy up to 25 weeks' gestation and with less than 3 cm. of cervical dilatation, the internal os procedure is again probably best and external os tracheloplasty second choice. After 25 weeks' gestation or with over 3 cm. dilatation, the external os "bridge" tracheloplasty is preferred. This is based on our 100 per cent success with 4 Grade II cases and only 25 per cent success with 4 other Grade III and IV cases. Even the external os failures prolonged pregnancy for an average of 6 weeks. This would be sufficient time to convert a Grade II to a Grade I case with a successful outcome almost assured. In addition, the simplicity of the external os procedure weighs heavily in its favor for

these milder Grade II cases. Postoperative recurrence of the cervical incompetence following Lash, Shirodkar, or other procedures, if not caused by onset of labor nor occurring before the thirtieth to the thirty-second week, should serve as indication for "bridge" tracheloplasty. An occasional Grade I case with a small fetus or multiple previous fetal losses might occasionally call for "bridge" tracheloplasty up through the thirty-second week of gestation. Anatomic repair of old cervical lacerations should be incorporated into the various procedures whenever feasible. Present methods of mid-cervical operations carry too low a success rate to be highly recommended.

Summary

1. Two techniques of external os surgical procedure for cervical incompetence occurring during pregnancy are presented, "bridge" tracheloplasty being the preferred one.

2. A method of grading the severity of this disorder is suggested.

3. Ten cases have been presented with 70 per cent success. Of these, 2 managed nonsurgically had 100 per cent success and 8 required operation with 63 per cent success.

4. Management of the incompetent cervix is suggested. Operation is indicated by vaginal proof of cervical incompetence during pregnancy and by positive history of 2 or more fetal losses from the disorder. Appropriate surgical techniques are discussed.

We wish to express our gratitude to Mrs. Wayne F. Baden for her patience and kindness in devoting her secretarial effort to the preparation of this manuscript. We also wish to thank Drs. H. C. McGrede, Jr., H. C. Henderson, Jr., and James E. Gleichert for contributing their cases to this series.

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Discussion

DR. CHARLES BRASELTON, JR., Fort Worth, Texas. Dr. Baden is to be commended on his unique and new approach to the surgical treatment of the incompetent cervix, an important condition, the proper detection and correction of which will improve fetal salvage and make happy, grateful parents out of depressed, lonesome married couples.

The diagnosis of this condition is quite important, else the proper patient will be overlooked and the wrong patient operated upon. The author has well defined and described this clinical entity and its signs and symptoms.

Our experience with this procedure entails 5 patients, all having a history of middle trimester abortions characterized by silent rupture of membranes followed by labor and delivery. One case was unsuccessful. The ligature material used in this case was polyethylene tubing and we feel that this material stretched sufficiently to allow cervical dilatation and subsequent rupture of the membranes about 3 weeks after operation. Removal of the polyethylene tubing allowed spontaneous miscarriage.

The ligature material used in our second case was polyethylene tubing containing a strand of No. 5 braided silk. In our last 3 cases we used Mersilene, a polyester fiber manufactured by Ethicon, as our ligature material and employed the technique as described by Barter and associates in March, 1958, *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*.

Our 4 successful cases had a total of 16 pregnancies with only 4 living babies before operation. Since cervical closure, there have been 4 living babies from 4 pregnancies, each case being successful. Cervical closure was performed at 17, 25, 18, and 14 weeks, respectively, and the pregnancy terminated by cesarean section at 38 weeks for 3 patients and at 36 weeks for one patient with ruptured membranes. Pregnancies were carried an average of 19 weeks after cervical closure.

The procedure has been simple with little blood loss and complete ambulation by one week post operation.

Patients for this procedure must be carefully selected as the operation is no panacea for the treatment of all abortions. If indiscriminately done, anatomical and psychological trauma results with no improvement in the ability of the patient to ultimately deliver a viable infant.

The most striking feature in the history of such pregnancies is the sudden loss of amniotic fluid between the sixteenth and the twenty-eighth week of pregnancy not preceded by painful contractions. The next most convincing means of proving incompetence of the cervix is to examine the patient weekly during pregnancy. When the condition is present, the cervix becomes effaced and dilated between the fourteenth and the twenty-sixth week. This process may take place slowly over several weeks, or, occasionally, rapidly over a week's time.

Needless to say, this procedure followed by cesarean section, is an expensive one for the patient, but the extreme gratitude of these patients warrants such expense, for in their opinion they have been cured of a practically hopeless situation.

We have had no experience with Dr. Badens' external os closure, but have seen a movie of Shirodkar's operation, similar to Barter's, performed successfully in the presence of a 3 to 4 cm. dilatation and bulging membranes.

The advantage of this operation over Dr. Baden's are: (1) ambulation, except for immediately postoperatively, is unrestricted; (2) it is a permanent type procedure ideally performed only one time for several subsequent pregnancies.

The disadvantage is that cesarean section must follow.

DR. ERWIN O. STRASSMANN, Houston, Texas. It is a rare occasion in one's life that one has

the privilege to discuss a new operation in our specialty. You and I just witnessed a new approach to the problem of the incompetent cervix during pregnancy.

By practically closing the external os, the authors created what might be called a line of *last* resistance against the protruding bag of waters. The construction of a bridge, leaving small openings for drainage on either side, reminds one of the LeFort operation for closure of the vagina. The "bridge" tracheloplasty has in cases of cervical incompetence prolonged the pregnancy by an average of 6 weeks. In 8 patients thus treated 63 per cent success, that is, living infants, was reported. This is a remarkable result considering the fact that the first and *main* line of resistance, that of the internal os, had necessarily vanished and was not restored surgically.

It seems from the results obtained that the closure of the external os with its limited duration is most effective in the *last* trimester, when it is just a matter of 6 to 8 weeks to reach viability of the fetus. In this respect, the new bridge operation can be regarded as a welcome supplement to the already popular closure of the internal os, which is preferably done during the *second* trimester.

We have, of course, no experience with the new operation of Baden and Baden, but we would like, at this time, to report shortly our experience with the closure of the internal os by the method of Shirodkar.

"*Simplex sigillum veri.*" Simplicity is the sign of truth. To put a purse string around the internal os in cases of an incompetent cervix is such a truth. It is surprising that nobody ever thought of doing it before.

I have had 7 cases so far, 2 during pregnancy, five prophylactically between pregnancies. The 2 patients operated upon *during* pregnancy carried up to the thirty-eighth week and had living babies by elective cesarean section. Six more operations were performed, during pregnancy, at the Hermann Hospital, Houston, by other staff members. Four of the patients had living infants. Two pregnancies ended prematurely with a dead fetus shortly after the operation. The total outcome of 8 Shirodkar oper-

ations done during pregnancy in our hospital is therefore that 6, or 75 per cent, met with success, which is the identical figure Shirodkar obtained in a much larger series.

Concerning the technique, we feel that the unabsorbable and nonirritating Dacron band or Mersilene is the material of choice. Braided silk with its potential foreign body reaction and homogenous fascia, requiring a primary operation, are obsolete. The authors rightfully stress the point that, following any operation for an incompetent cervix, rest, sedatives, and hormones are advisable to arrest or prevent labor. As to hormones, we found a daily dose of hydroxyprogesterone coproate (Delalutin), 2 c.c. intramuscularly, superior to Lutrexin.

Another point has to be made here. An incompetent inner os is not always the result of a previous obstetrical lesion. It may be a congenital weakness in a hypodeveloped uterus. In these instances the hystrogram shows no defect because the incompetency of the cervix is strictly functional and not apparent before pregnancy.

For this reason an obstetrical history of multiple late abortions or premature labor is the best indication for the Shirodkar operation to be done either prophylactically or during the second trimester. In the last trimester the new method of the authors may prove to be preferable to the encircling band around the internal os, even without the presence of old, deep lacerations. To add 6 to 8 weeks to the duration of pregnancy would be all that is required.

A rupture of the uterus in the presence or even after the removal of the implanted strip is always a potential threat which the closure of the external os does not carry to that extent. Another advantage is that vaginal delivery can always be accomplished simply by separation of the bridge.

The recognition of the incompetent cervix as an obstetrical complication and its successful surgical management is a milestone in the history of our specialty. I hope that the new operation will stand the test of time and that the names of Baden and Baden will be added to those of Lash and Shirodkar in our obstetrical hall of fame.

The incompetent internal os of the cervix: diagnosis and treatment

A. F. LASH, M.D.

Chicago, Illinois

THE incompetent internal os of the cervix is an abnormally enlarged canal at the corporocervical junction; the degree of its enlargement varies. When the enlargement is of a moderate or severe degree, repeated abortions will occur, particularly during the second trimester, regardless of whether the patient is in a constant supine position or whether she has been subjected to medical therapy. Placenta previa and hydrocephalus have been known to act as spontaneous corrective conditions. Otherwise, only surgical therapy can render the cervix competent to retain subsequent normal pregnancies.

My studies of the incompetent internal os of the cervix reveal that its rapid and traumatic dilatation is due to: (1) overzealous dilatation of the cervix for diagnostic curettage or abortion; (2) precipitate deliveries due to tumultuous uterine contractions (spontaneous or drug-induced) or to obstetrical operations involving forceps or version and extraction; or (3) poor uterine wound healing due to improper coaptation or infection after a cesarean section (abdominal or vaginal).

While these procedures obviously occur more often than does the incompetent cervix, one is led to assume a good number may heal primarily without leaving a scar or defect in the circumference of the corporocervical area. This latent weakness may

explain the occasional unexpected and surprising disappearance of the dilator or curette through the wall of the uterus at the internal os during a subsequent dilatation and curettage and it also may be the basis for the so-called spontaneous rupture of the uterus in normal delivery when there is no cephalopelvic disproportion.

Review of the literature

In 1948, Palmer and Lacomme² discussed the question of "gaping" of the internal orifice of the cervix as a cause of repeated second-trimester abortion. They reported a successful outcome in a patient who had had 3 second-trimester abortions. In 1950 Palmer³ described manometric hystero-graphy in a series of patients, which indicated that anatomic variations of the cervix may occur either on the basis of uterine anomalies or secondary to childbearing.

Fisher,⁵ in 1951, concluded from a review of the literature and his own reported cases of childbearing following extensive cervical amputation that there was a dramatic increase in the rate of premature delivery and late abortion following this operation.

In 1952, Asplund⁶ published his combined hystero-graphic and arteriographic studies; these demonstrated variations in the isthmus zone, which he considered to be physiologic, based on hormonal variations.

Borell and Fernström⁷ described their studies of the sphincter mechanism of the isthmus uteri in 1953.

From the Department of Obstetrics and Gynecology, College of Medicine, University of Illinois, and Michael Reese Hospital.

Diagnosis

The diagnosis of the incompetent internal os of the cervix is based on a history of repeated abortions, especially during the second trimester of pregnancy. These repeated or habitual abortions are characterized by a usually painless presentation of the bulging membranes at the external os of the cervix, and this is followed by rupture and relatively painless expulsion of the baby. Occasionally, slight spotting or increased cervical secretions may precede the rupture. When a pregnant woman is examined with a speculum there is the intriguing sight of the bulging membranes and the occasional moving extremity. In the nonpregnant state, however, physical examination will reveal no abnormality. Only by exploration of the cervical canal with a uterine dressing forceps or Hegar dilator is the lack of resistance at the internal os found.

Palpation of the external circumference of the cervix at the level of the internal os, with a sound or uterine dressing forceps in the canal, will demonstrate a defect or thinned-out area, either anteriorly or laterally. This point of decreased thickness is the site of the injured or lacerated cervical wall which healed with the wide scar resulting. This abnormal internal os can also be demonstrated by hystero-grams and by the balloon method.⁸

These confirmatory roentgen studies are necessary if the abnormal orifice is only of slight or moderate degree, because anomalies and hypoplasia of the uterus as well as submucous fibroids may produce habitual abortions.

Principles of therapy

Treatment of the incompetent internal os of the cervix aims to restore the normal caliber of the isthmus either by closure of the defect produced by the trauma or by excision of the scar tissue in the area of the defect, which may vary from 1.5 to 2.0 cm. in width and from 2.5 to 3.5 cm. in length, while the thickness varies from a thin center to a few millimeters in thickness with edges equal to the thickness of the cervical wall.

The exceptional defect is the one extending from the external os through the internal os. This type of laceration is obvious and does not escape detection like the above-described type.

One should always consider the prevention of this condition; under prophylaxis, the cervical dilatation preceding diagnostic curettage should not exceed a No. 9 to a No. 11 Hegar dilator in order not to produce lacerations and defects in the internal os ring. Nontraumatic deliveries of the head may be accomplished by avoiding the excessively strong contractions in Pitocin-accelerated labor, difficult forceps delivery of the head, or too rapid extraction of the aftercoming head. The prevention of infections in cervical repairs can be achieved by eliminating the infection before, during, and after operation by the prophylactic use of antibiotics. These precautions are especially noteworthy during abdominal or vaginal cesarean section in the presence of prolonged labor and during prolonged rupture of the amniotic sac where intrapartum infection is so common.

Medical measures include rest in bed during and after the period of pregnancy when the previous habitual abortion occurred; this is augmented by sedation and possibly by a muscle relaxant (Delalutin or Relaxin⁹).

I am fully aware of the fact that in the mild degree of incompetency of the internal os bed rest from the third month to term may suffice to prevent an abortion. A placenta previa may also act as a support. Others have suggested the placing of ligatures and fascial strips around the cervix during a pregnancy complicated by a dilated cervix with bulging membranes.¹⁰⁻¹³ I know of only two instances in which the repair was done during pregnancy, with but one successful result. It has been my experience, however, that a defect of moderate or marked degree will always produce an abortion, even if the patient is in the supine position throughout the pregnancy. The healing properties of the cervix or the quality of the sutures may not always

achieve this expectation at the first attempt and occasionally repeated repairs may be necessary. The results of the surgical management of 85 cases of repeated abortions with an established etiology of incompetent internal os of the cervix form the basis of this report.

Materials and method

In the preoperative evaluation of the patient the general reproductive status of the individual must be considered in the prognosis of the surgical result. In my series, the ages of patients varied from 20 to 42 years; about 60 per cent were under 30 years of age, a little over 90 per cent were under 35, and only 6 patients were over 35. Only 3 of the women over 35 became pregnant; 2 delivered full-term babies and one is currently pregnant. In none of the patients was infection of the cervix present. Therefore no local preparation was necessary and only the optimum time for operation which is midcycle or immediately after the termination of a pregnancy was awaited. I wish to emphasize that operation is indicated only after the demonstration of the incompetent internal os.

The surgical technique which has been described in detail in my previous publications^{1, 8} varied from imbrication sutures over the defect in the anterior wall to wedge-shaped excision of the scar and closure or more extensive excision which started at the external os and encompassed the scarred defect area, producing an anterior hysterotomy wound to be closed. These repairs were carried out in patients immediately following delivery or in non-pregnant women. The sutures were either No. 2 chromic catgut for primary repair in normal tissue or tantalum wire for repeat repairs or when the tissue appeared relatively avascular. As a rule, two layers of interrupted sutures were inserted. In those instances where there was an associated descensus or prolapsus uteri a Manchester plastic operation was also performed.

Current technique. Reflection of the blad-

der is accomplished by a semicircular incision through the vaginal wall at the anterior reflection of the vaginal wall over the portio; when the bladder is freed from the anterior cervical wall, the basis of each cardinal ligament is visualized. With a dilator in the cervical canal the extent of the defect can be determined. At the upper edge or a little above the defect a stay suture is placed for guidance. The defect is excised in a longitudinal oval wedge of the anterior or lateral cervical wall and the full thickness of the cervical wall is demonstrated. The wound is closed with two layers of interrupted No. 2 chromic catgut sutures. During this closure the dilator is in place to avoid suturing the canal closed or producing strictures by inadvertently passing sutures through the posterior wall. The dilator No. 4 is withdrawn as the sutures are tied. There is immediate evidence of narrowing of the internal os when it is tested with the dilator. The anterior portions of the cardinal ligaments are sutured over the cervical sutures, thus, they are covered and the descending uterus is elevated. The vaginal wound is closed with No. 0 chromic catgut. The No. 2 chromic catgut is used in the repair because the cervix has poor healing qualities and the heavier catgut gives greater security. No. 1 chromic catgut has been used but not successfully.

Postoperative prophylactic antibiotics are utilized in a certain number of patients. The patients are ambulatory in 24 hours and go home in 4 or 5 days. Coitus is prohibited for one month and contraception suggested for 6 months, since failures have occurred in a few patients who became pregnant within 2 or 3 months of the repair.

Results

Table I gives the incidence of successful pregnancies—47 term or near-term—in 57 pregnancies occurring from 2 months to 3 years after the repair. There has been only one instance of breakdown of the wound during the course of a delivery; this was recognized and resutured. All the full-term

Table I. Postoperative results

	No. of patients
Operated upon	85
Subsequent pregnancies	59*
Term or near term	47†
Total viable babies	67
Current pregnancies	4
Spontaneous abortions	5
Induced (criminal) abortions	1
Hydatid moles	1
Death, fifth month of pregnancy (pneumonia)	1
Nonpregnant (more than one year after operation)	9
Too recent (less than one year after operation)	12
Lost	5

*Number of patients who became pregnant.

†Number of patients who went to term or near term with viable babies one or more times.

pregnancies before the repair occurred before the repeated abortions. The abortions which occurred after the repair were early or first-trimester abortions with the exception of one, which occurred in the second trimester. In this case a defect was still present and therefore the repair was a failure. Secondary repair proved successful. In 3 other cases failures occurred as judged by the presence of defects although these were all late first-trimester abortions. One of these failures required a second repair and 2, a third. All these subsequent repairs were performed at the time of the abortion.

Of the 47 deliveries, 31 were vaginal and 16 by cesarean section (Table II). The guide for choosing the route of delivery was the station of the head at the onset of labor. If labor was established with the head high, the abdominal route was chosen; if the occiput was in the pelvis, that is, at station 0 or below, vaginal delivery was anticipated, and it was accomplished in all patients so judged.

Table II. Types of delivery in 47 patients

Method of delivery	No. of patients	No. of deliveries		
		1	2	3
Vaginal route	31	19	8	4
Cesarean section	16	12	4	0

All the uterine cavities were explored at the time of the delivery. The cervix was also inspected and explored 6 weeks post partum; in spite of a distorted appearance of the portio, the internal os was found to be properly closed.

Catgut sutures were used in the majority of instances and tantalum wire was utilized only in the presence of much scar tissue or in repeated operations. There were 3 failures even with tantalum wire.

The postoperative course was smooth in all cases and prolonged in only one patient whose bladder was injured, a catheter remaining in the bladder for 10 days. In only 2 patients was subsequent probing of the cervical canal necessary because of acquired dysmenorrhea. Menstrual function was otherwise undisturbed. When reproduction does not follow within a reasonable time, the usual fertility studies must be instituted.

Summary and conclusion

Eighty-five women had incompetent internal os repairs; only 80 were followed postoperatively. Fifty-nine became pregnant and 47 came to term or near term one or more times, yielding viable babies; 2 of the patients had secondary and 2 tertiary repairs. Of those patients who became pregnant and progressed to term or near term there was an 80 per cent yield.

In conclusion, the management of this pathological condition merits serious consideration in view of the almost hopeless state that exists if no permanent correction of the incompetency of the internal os is carried out. Occlusive surgical procedures performed during pregnancy are not permanent corrective therapy and are justified only as an emergency measure when the patient is seen for the first time during a threatening abortion with a bulging or visible bag of waters and with a dilated or dilating internal os of the cervix.

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Cervical incisions in present-day obstetrics

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SINCE the introduction by Dührssen of cervical incisions as a means to effect complete dilatation and subsequent vaginal delivery, this procedure has been the subject of much controversy. Several authors, notably Hunt and McGee¹ in 1936, Huber² in 1939, Douglass and Graves³ in 1948, and Evans and Stander⁴ in 1954, have emphasized the place in obstetrics where cervical incisions could and should be used with favorable results to both mother and baby. More recently, Cope,⁵ in the British literature, reviewed 13 cases in which cervical incisions were used. In contrast to most American obstetricians, he favored incisions made at 3 and 9 o'clock rather than the conventional 10, 2, and 6 o'clock. There was no perinatal mortality in his small group of patients; 4 of the 13 presented the problem of cervical dystocia as has been outlined by Jeffcoate and Lister.⁶ Cervical incisions have been advocated by these latter authors as one possible solution of this dilemma. Rubovits and Cooperman⁷ presented the experience of the Chicago Maternity Center in the use of "Dürrssen's incisions in prolonged labor." Deliveries in their series were conducted in the home. Their over-all incidence in a 20 year period was 0.27 per cent with an uncorrected gross perinatal mortality of 15.4 per cent. There was one maternal death in their series.

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The Chicago Maternity Center delivers approximately 3,000 women per year, the vast majority being cared for in the home. Those patients who require hospitalization are transferred almost exclusively to the Chicago Wesley Memorial Hospital. It is the purpose of this paper to review the total experience of cervical incisions at this hospital from Jan. 1, 1953, to June 30, 1958. This review seems timely since, for one thing, this period represents a time when the administration of intravenous Pitocin as a means to overcome uterine inertia has become commonplace. It was thought that this factor plus more liberal use of cesarean section in cases of fetal distress might well relegate cervical incisions to the museum where the Voorhees bag and high forceps now reside. We shall attempt to determine if this assumption is correct.

Clinical material

In the 5½ years under review there were 59 instances where cervical incisions were used to effect complete dilatation and/or delivery. Of these 59, 19 were in Chicago Maternity Center patients and 40 in private patients. These Chicago Maternity Center patients were not included in the report by Rubovits and Cooperman.⁷ During this period 10,191 women were delivered, of whom 9,301 were private or Wesley Service patients (clinic patients who had prenatal care and delivery at the hospital) and 890 were Chicago Maternity Center patients delivered at Wesley. The over-all incidence of cervical incisions was 0.57 per cent (Table I) with an incidence of 0.42 per cent, ex-

clusive of Maternity Center patients. Though the numbers of this series are small, it is significant in some aspects to analyze separately the private and Maternity Center patients. There were no Wesley Service patients in our series.

Table I. Incidence of cervical incisions (Jan. 1, 1953—June 30, 1958)

	Chicago Maternity Center	Wesley Clinic and private patients	Total
Deliveries	890	9,301	10,191
Cervical in- cisions	19	40	59
Incidence	2.14%	0.43%	0.57%

The procedure has been used rather consistently over the period in question, as is attested to by the fact that there were 28 cases in the first 3 years of the study and 31 cases during the latter 2½ years. In the earlier years, the Chicago Maternity Center patients were the responsibility of one obstetrician, but in the latter period four other obstetricians have utilized cervical incisions to facilitate termination of labor in these patients. In the private group a total of 11 obstetricians have used cervical incisions at least once. One of these, however, accounts for 50 per cent of the total private group.

As in most other series, the majority of patients were primigravidas with the usual age distribution (Table II). Also, as would be expected, the average age of the Chicago Maternity Center patients is younger than that of private patients.

Fifty-four of the 59 patients were at term (estimated between 38 and 42 weeks), three were preterm (33 to 35 weeks), and two were considered to be at 44 weeks gestation. Fifty-eight of the 59 infants were in cephalic presentation at the onset of labor; the other was in breech presentation. Of those which were cephalic, there were a large number which were either left or right occipitoposterior. However, the

total number of women who entered labor with the fetal head engaged is greater than those who entered with the fetal head unengaged. This is in contrast with the findings in previous papers and is so because of the findings in the private group (Table III). At least a partial explanation for this will be found when the indications for the operation are examined.

Premature rupture of the membranes was not a striking finding in this group of patients, there being only 5 who had ruptured membranes for over 24 hours prior to the onset of labor. Another 8 patients had ruptured membranes for less than 24 hours before labor ensued, and the remainder had ruptured membranes during labor. The latter were equally divided between spontaneous and artificial rupture.

Table II. Age and parity of patients

Parity	Age (range and average)		
	Chicago Maternity Center (16-37, ave. 23.6)	Private (19-43, ave. 28.8)	Total (16-43 ave. 27.1)
0	16	31	47
1	0	5	5
2	1	2	3
3	0	1	1
4	1	1	2
5	1	0	1

Table III. Position and station of fetal head at onset of labor

	Chicago Maternity Center	Private	Total
Posterior	15	27	42
Transverse	3	11	14
Anterior	1	1	2
Unengaged	12	12	24
Engaged	7	27	34

The technique of cervical incisions has been well documented in both papers and texts.⁸ Suffice it to say that saddle block anesthesia was used in 42 instances, general

anesthesia in 7, pudendal block in 8, and parasacral anesthesia in 2. The cervical incisions were accomplished before the episiotomy was performed, and no rotation or attempted forceps delivery was done before the incisions. The incisions were carried to the vaginal vault and repaired after delivery with either interrupted or continuous catgut sutures. The number of incisions varied from three (done at 10, 2, and 6 o'clock) to one (Table IV), depending partially upon the cervical dilatation. If the posterior lip of the cervix was not available, two incisions at 10 and 2 o'clock were sufficient to effect complete dilatation without untoward effects.

The conditions that must be present before cervical incisions are attempted must be emphasized. They are: (1) first and foremost, the cervix must be completely effaced; (2) the membranes must be ruptured; (3) the head in cephalic presentation must be well engaged; and (4) there must be no cephalopelvic disproportion. Cervical dilatation is of no importance in deciding whether or not to perform cervical incisions if the above conditions are met (Table IV). In this series, dilatation under 6 cm. did not increase the complications of the operation.

Table IV. Cervical dilatation and number of incisions at time of operation

	Chicago Maternity Center	Private	Total
Dilatation			
3 cm.	1	0	1
4 cm.	2	2	4
5 cm.	2	6	8
6 cm.	5	12	17
7 cm.	4	13	17
8 cm.	5	7	12
No. of incisions			
3	12	24	36
2	5	14	19
1	2	2	4

Indications

For an operation such as cervical incisions to be justifiable and remain in the armamentarium of the obstetrician, there should be

Table V. Indications for cervical incisions—no progress in labor; no fetal distress

	Chicago Maternity Center	Private	Total
No. of cases	17	19	36
Total first stage			
Range	12-52	10-57	10-57
Average	34.8	21.4	27.7
Hours of no progress			
Range	2-29	2-15	2-29
Average	12.7	7.5	10.0
I.V. Pitocin			
No. of cases	2	7	
Hours without progress			
	1½*-2	2-7†	

*Fetal heart tones dropped below 100; Pitocin stopped.

†Also one other patient who developed uterine tetany after the beginning of Pitocin administration; Pitocin stopped immediately.

circumstances wherein this procedure should be better than or at least as good as an alternate approach. The indications and then the end results of the procedure in this group of patients, therefore, becomes all-important. In an attempt to discover if, when, and why cervical incisions should be done, the indications were categorized on the following basis: (1) no progress in labor, but without apparent fetal distress; (2) normal progress in labor, but evidence of fetal distress; and (3) no progress in labor, associated with apparent fetal distress. This classification may be somewhat arbitrary, for who can be certain that after 24 hours of labor the fetus is in no distress even though heart tones remain normal and no meconium appears in the amniotic fluid. For purposes of discussion, however, this classification seems to be of value. It becomes apparent at once that those patients from the Chicago Maternity Center are quite comparable to the series of patients presented by Rubovits and Cooperman whose labors were terminated by cervical incisions and forceps in the home. It also becomes apparent that the conditions present in a group of private patients were quite different, even though the indication for cervical incisions was the same, i.e., no progress in labor but without fetal distress (Table V). In essence, the Maternity Center

patients were in labor longer and remained without progress for longer periods of time than did the private patients. These factors probably account for the absence of the administration of Pitocin in all but 2 of the 17 patients from the Maternity Center, for in most cases delivery from below was deemed advisable once cephalopelvic disproportion was ruled out. The private patients who received intravenous Pitocin had adequate trial of this medication before it was discontinued. Those who did not receive Pitocin were deemed to have had adequate labor but without progress. There were no cases of Pitocin inductions in this group.

The group of patients in whom cervical incisions were performed because of fetal distress number 16 in the private group and one in the Maternity Center group. These are tabulated in Table VI. Fetal distress was diagnosed by persistently slow and irregular fetal heart tones not benefited by the administration of oxygen and the Trendelenburg position, persistently slow fetal heart tones below 100 per minute, or persistently rapid heart tones over 180 per minute. Most of these were associated with passage of meconium. The length of distress varied from less than 30 minutes to 4 hours in one case. There was no case of fetal

Table VI. Indications for cervical incisions—normal labor; fetal distress

	Chicago Ma- ternity Center	Private	Total
No. of cases	1	16	17
Slow fetal heart tones ($<100/\text{min.}$)		3	3
Rapid fetal heart tones ($>180/\text{min.}$)		2	2
Slow and irregular fetal heart tones	1	11	12
Cause of distress			
Abruptio placentae		4	4
Occult prolapse of cord		3	3
Cord around neck		1	1
Torsion of cord		1	1
None apparent	1	7	8

Table VII. Indications for cervical incisions—no progress in labor; fetal distress (private patients)

No. of cases	5
Total first stage	
Range	6-16
Average	10.0
Hours of no progress	
Range	1-3
Average	2.0
Slow and irregular fetal heart tones	4
Meconium only	1

distress diagnosed from the passage of meconium alone.

One patient in the group had a Pitocin induction with fetal distress diagnosed at 8 cm. dilatation. Three others had Pitocin stimulation after discovery of slow and irregular heart tones. In all three the signs of fetal distress became more pronounced before complete dilatation of the cervix was effected. It is not unusual that the cause of fetal distress is not apparent after delivery, and such was the case in 8 of the 17 cases.

There were 5 private patients who had what is considered a combination of no progress in labor and fetal distress as an indication for the cervical incisions. From Table VII it is apparent that fetal distress was the more important factor since the total labor and hours of no progress were relatively short. One of these patients had a Pitocin induction with failure of progress after 7 cm. dilatation. In this patient, there was much meconium in the amniotic fluid but fetal heart tones remained good. In the remaining 4 patients there were slow and irregular fetal heart tones. Irregularity was noted for over 30 minutes in all 4; even so, the cause for fetal distress was not apparent in any patients in this category.

There remain 2 patients not included in the above discussion of indications. One patient had a spontaneous premature breech delivery to the scapulae, and the cervix was then found tightly applied to the head. A cervical incision at 6 o'clock permitted delivery. The other patient was followed at

home with a prolonged labor of 48 hours' duration and fetal death. Delivery in the hospital was accomplished by cervical incisions from 4 cm. dilatation, craniotomy, and extraction.

Immediate results

Of the 58 infants in cephalic presentation at the time of cervical incisions, 25 were delivered from a plus 1 station, 26 from plus 2, and 6 from a plus 3 station. There was one instance of failed forceps in an unrecognized cephalopelvic disproportion in a Maternity Center patient. The infant was delivered by cesarean section. There were two sets of twins, giving a total of 60 live births. Forty-two of these required rotation from a posterior position and 11 from a transverse position before delivery was accomplished. There was one fetal death, which has been alluded to, and one neonatal death occurring in an infant on the ninth day of life due to streptococcal bronchopneumonia. The mother of this infant developed an intrapartum sepsis at home and was admitted to the hospital after 42 hours of labor. The fetal death occurred in 1953 and the neonatal death in 1954. The total perinatal mortality in the entire group of patients is 3.27 per cent. There was no perinatal mortality among the private patients and there was no maternal mortality in the total group.

Six of the infants weighed under 2,500 grams and 6 weighed over 4,000 grams. Resuscitation of over 3 minutes was required in 5 of the 60 liveborn infants. There were two instances of cephalohematoma but no other indication of fetal trauma.

Table VIII. Postpartum hemorrhage (over 400 c.c.)

Cause	No. of cases
Extension of incision	2
Uterine atony	4
Vaginal laceration	9*
Bleeding sinus, lower uterine segment	1
Abruptio placentae	1
Total	17

*One also had abruptio placentae.

Immediate postpartum complications included extension of the cervical incisions with postpartum hemorrhage in 2 cases. In each case, one incision was involved in patients in whom three incisions had been made. In addition, there were 15 other instances of postpartum hemorrhage, as outlined in Table VIII. There were only 2 cases of postpartum sepsis as defined by usual standards; both of these occurred in Maternity Center patients who had intrapartum sepsis. There were no cases of delayed puerperal hemorrhage.

Late results

On follow-up examination 29 of the private patients were said to have had good healing of the cervix. Three were said to have healed fairly well, and 4 were reported as healed poorly in one or more of the incisions. Four patients were not reported. Among the Maternity Center patients, 11 were reported as having healed well, 4 fairly well, and one poorly. Three were unreported.

Six of the private patients subsequently have been delivered of 8 infants without complication. In addition, 4 have been delivered who exhibited a cervical laceration at the site of one of the previous incisions. One patient had a cesarean section because of an abruptio placentae (which, with slow and irregular heart tones, was the indication for the original cervical incisions), and one patient was operated on because of an ectopic pregnancy. Four other private patients are now pregnant and undelivered.

Of the Maternity Center patients, 5 have delivered 6 infants without complication.

Comment

Although cervical incisions rightly no longer play the role they once did in complicated obstetrics, it seems obvious to the author that they should not be relegated to antiquity. As time goes on and obstetrics becomes more refined, perhaps their role should even be less; but in the isolated case where conditions are ideal and the situation calls for delivery in the face of an incom-

pletely dilated but completely effaced cervix, there probably will always be a place for this procedure. Certainly in the presence of fetal distress wherein vaginal delivery would be relatively easy if the cervix were completely dilated, cervical incisions and delivery are the procedures of choice.

The diagnosis of fetal distress today depends upon the findings of persistently slow or slow and irregular fetal heart tones usually with meconium-stained amniotic fluid. If these findings persist after the usual conservative management with oxygen and Trendelenburg positioning, delivery is mandatory. At least in our institution, fetal distress is becoming more and more common as an indication for cesarean section. It seems only logical that if fetal indications are present which necessitate delivery and the conditions are present which are right for cervical incisions, then cervical incisions should be used. There is no question that this method affords the most rapid mode of delivery and in a given case may, therefore, be life-saving. Of course, such a procedure should be used only if it is safe for the mother and baby, and the results experienced by us seem to indicate that it is. Obviously, some cases of fetal distress in this series would not have resulted in perinatal mortality if labor were allowed to continue. However, in the individual case, it would indeed take a seer to pick these patients out and then wait for complete dilatation.

That the cause for fetal distress was not found after delivery in many of our cases does not negate the necessity for delivery. The fault lies in our present-day crude methods of diagnosing fetal distress. Until these methods are refined, speedy delivery is our only answer whether it means vaginal or abdominal delivery.

The other broad indication in which cervical incisions were utilized in this series was in those labors where progress came to a halt. Many and complex are the factors which cause this condition. It is beyond the scope of this paper to comment on these in detail. Certainly, relative cephalopelvic dis-

proportion, so-called positional dystocia, and the elusive cervical dystocia all played their part. Intravenous Pitocin has done much to overcome these complications. That it was used in only 2 of the 19 Maternity Center patients is due to the fact that these patients for the most part had long labors with long hours of no progress. Some of these patients were septic; all were exhausted. Few obstetricians would use Pitocin under these conditions, and few will deny that delivery was indicated.

In the private group of patients conditions were different; in many of these, Pitocin was not used since contractions were good, and yet progress was nil. The failure of Pitocin in others should not be emphasized, but it should be emphasized that Pitocin is not a panacea, and in some few cases it will not work. Perhaps in these few cases it is wise to have the trump card of cervical incisions.

The major complication in this series was vaginal lacerations. This is undoubtedly secondary to midforceps application and extraction. It should not be a factor to invalidate a procedure, however, since such lacerations are not rare in low or even outlet forceps deliveries.

We are not championing the case for cervical incisions as anything more than an operation to be used rarely and to be used only when conditions and indications are right for it. Since these occasions do and will arise, however, it is unfortunate if obstetricians in training today are taught nothing about this operation other than to fear it.

Summary

1. Fifty-nine cases of cervical incisions, occurring in a 5½ year period are presented.
2. There was one fetal and one neonatal death in infants delivered after cervical incisions. There were no maternal deaths in the group.
3. The conditions and indications for cervical incisions, and their role in operative obstetrics, are discussed.

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Discussion

DR. D. N. DANFORTH, Evanston, Illinois. The average obstetrician is a very critical and dogmatic physician. While there are none who survey their own work with so critical an eye, one rarely finds unqualified agreement on the management of even a simple obstetrical problem. In accordance with this unrestrained type of thinking, the critical obstetrician may interpret differently any published obstetrical figures and any listing of conditions or results or indications for a given procedure. But rather than consider these in particular, it is my purpose to make certain generalizations based on the major theses of this paper.

The 40 cervical incisions among 9,301 Wesley clinic and private patients should be contrasted with 7 such operations among 10,361 Evanston Hospital clinic and private patients delivered during the same period. Although the figures are not given, it is possible their higher incidence of cervical incisions may reflect a cesarean section rate which is somewhat lower than our own incidence of 4.2 per cent for our last 10,000 deliveries. In any event, I do know that although there is this evident difference in certain of our techniques and principles, our final results, in terms of the ultimate objectives of a healthy mother and a healthy baby, are similar.

Certainly Dr. Carrow is to be congratulated for demonstrating beyond question that this operation, when judiciously performed by expert obstetricians, with the most meticulous attention to certain requisite conditions, is safe and can produce happy results. This is an important contribution. The operation does have a place in modern obstetrics, and, if used with full knowledge of its hazards, its contraindications, and its alternatives, it can provide in certain cases a solution which is better than that which is offered by any other technique or procedure.

A word of caution is necessary, however, lest the uninitiated infer that, since it is so very

easy to perform and since the results can be so very good, it may be undertaken casually whenever things seem to be slowed up a bit. To my thought, there is in all obstetrics no decision more serious; and there is no operation which may either directly or indirectly result in more horrendous damage to both mother and baby than may occur in the 5 or 10 minutes which follow the carrying out of this very simple operation.

The two main indications listed are lack of progress in dilation of the cervix, and fetal distress.

1. Coordinated, effective contractions are essential for cervical dilation and such coordinated contractions can occur only when there is proper fitting of the presenting part or an intact bag of waters to the lower pole of the uterus. This brings me to the trap set for the inexperienced, to wit, the belief that one deals with primary cervical dystocia when in fact it is cephalopelvic disproportion which prevents the head from fitting into the lower pole of the uterus. In such a case the operation of cervical incision may be very easy, but it is clearly contraindicated and may be followed by disaster.

2. With regard to the second major indication, fetal distress, this, too, requires the most careful and almost intuitive contemplation. One must first decide whether the shock of immediate delivery may be greater than the hazard of inactivity and, if instant delivery is decided upon, whether cesarean section might be less damaging to an embarrassed baby than cervical incision and extraction from the midpelvis. I think most will agree that, as a rule, cesarean section is preferable if fetal distress occurs midway through an otherwise normal labor.

In conclusion, I believe that Dr. Carrow has rendered a very significant service in establishing beyond question that cervical incision, in the most competent hands, can provide a safe and expeditious means of dealing with certain

cases of failure of progress and fetal distress. But I am also convinced that the decision to perform this operation is a very serious one indeed, and should properly be made only if there is no reasonable alternative.

DR. FRANK E. RUBOVITS, Chicago, Illinois. Obstetrics is a surgical discipline and an obstetrician should be fully qualified to carry out appropriate surgical procedures when he serves his patients. It would be unfortunate if obstetrics were reduced to the oversimplification of "Well, this patient is not going to deliver from below, so she shall be delivered from above." This stultifies the specialty and does a disservice to those who seek our care. Surgical discipline demands that the correct procedure be chosen in a given situation. The correct procedure is the one that will cure the patient, or patients, with the least trauma, both immediate and remote. That an operation is used seldom does not justify a surgeon's being unfamiliar and untrained in its use. In the conduct of cases such as those described by the author, the Dührssen operation fulfills these requirements.

Perhaps it is justifiable to emphasize again that the Dührssen operation, cesarean section, and intravenous Pitocin should not be, and are not, in competition one with one another. With a given set of conditions and an indication present for prompt delivery, the appropriate selection may be made from among these techniques if the obstetrician has evaluated the situation appropriately.

Let us assume that the incidence of cesarean section in the 10,191 deliveries in this series is approximately 3 to 4 per cent. Let us assume further that the incidence of the Dührssen operation is weighted significantly by the fact that difficult Chicago Maternity Center cases are channeled to Wesley.

Then let us assume that all of the patients delivered by the Dührssen operation had been delivered by cesarean section. This would add but one half of a percentage point to the

statistical incidence of cesarean section and would keep this incidence within "acceptable" limits. To me this indicates the shortcomings of our usual interpretations of obstetrical statistics. To obtain a less complacent but more realistic view of our end results, all cases of normal labor should first be excluded. Then the decimal points would bounce to the right. This, I believe, would be most useful in helping us to refine our indications and to contemplate our morbidity.

In the presence of fetal distress, the Dührssen operation seems exceptionally well suited under proper conditions. If time is of the essence this operation provides a means by which a fetus can be delivered with grace and finesse in the hands of a skilled operator. In the prolonged labor group this is equally valid, for certainly successful delivery through the natural passages is fraught with less risk to the patient than is cesarean section. It is especially in the prolonged labor group that cesarean section remains a relatively formidable operation in so far as postsurgical complications are concerned.

The use of intravenous Pitocin has, of course, obviated many Dührssen operations. I cannot resist noting, however, that in Table V, in which the data concerning the category of "No progress in labor; no fetal distress" is documented, in 2 cases intravenous Pitocin is noted to have been associated with evidence of fetal distress. Although this drug has a reasonable safety factor, its use may cause mischief that will on occasion make facility in the Dührssen operation essential—or at least highly desirable.

DR. CARROW (Closing). The two discussants alluded to our cesarean section rate which, I must say, is higher than 3 or 4 per cent in our hospital.

Regarding Dr. Rubovits' point on delivery in the presence of fetal distress, I wish to emphasize that cervical incisions often offer the most rapid mode of delivery.

Twin Ring Retractor for the postpartum cervix

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DURING obstetrical labor, lacerations of the cervix occur occasionally. When they do occur they should be sutured. Without the aid of an assistant to hold the cervix steady and fixed, it is difficult to put in the few sutures that are usually necessary. Because labor occurs at odd hours and because of other reasons an assistant during labor is usually unavailable. Therefore, an instrument, which is self-retaining (Figs. 1 and 2), has been devised to hold the cervix fixed during suturing. This instrument is a modification of the Twin Cervical Tenaculum¹ previously described which has been found useful in holding the cervix steady during cold conization of the cervix.

Technique

The knurled nut of the Twin Ring Retractor is loosened so there is complete freedom

of movement of the clamps. After a weighted speculum is placed in the vagina the cervix is grasped with a straight sponge forceps and is pulled toward the vaginal vestibule. The right side (to operator) of the cervix is then grasped with the right clamp of the Retractor; the left side of the cervix is grasped with the left clamp. Then, the straight sponge forceps are detached. The clamps of the Retractor are spread as far as possible, and the knurled nut is tightened.

The clamps of the Retractor will also spread the vaginal vestibule apart, and good visibility as well as good fixation of the cervix for suturing will be obtained (Fig. 2). If the laceration is exactly transverse the Retractor may be fastened to the cervix somewhat obliquely so that the blades of the clamps are not on the torn edges of the cervix. It is not necessary to hold the handle

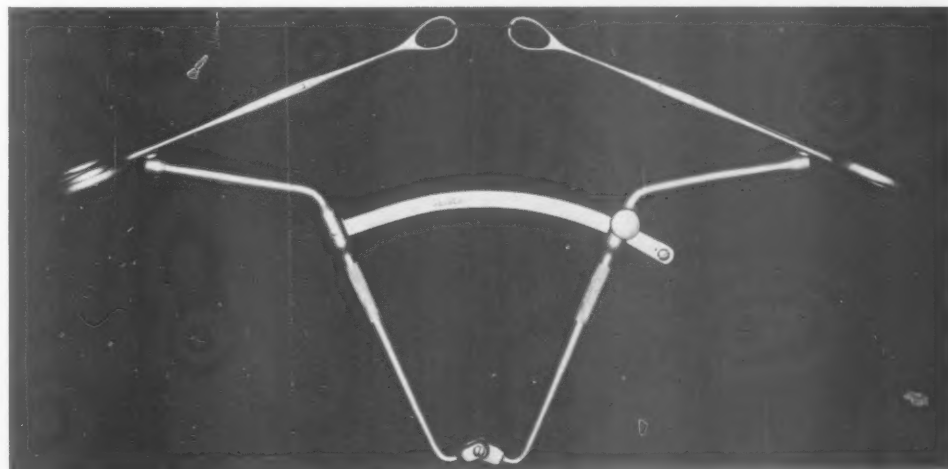


Fig. 1. Cervical Twin Ring Retractor. (Manufactured by Milex Products, Chicago, Illinois.)

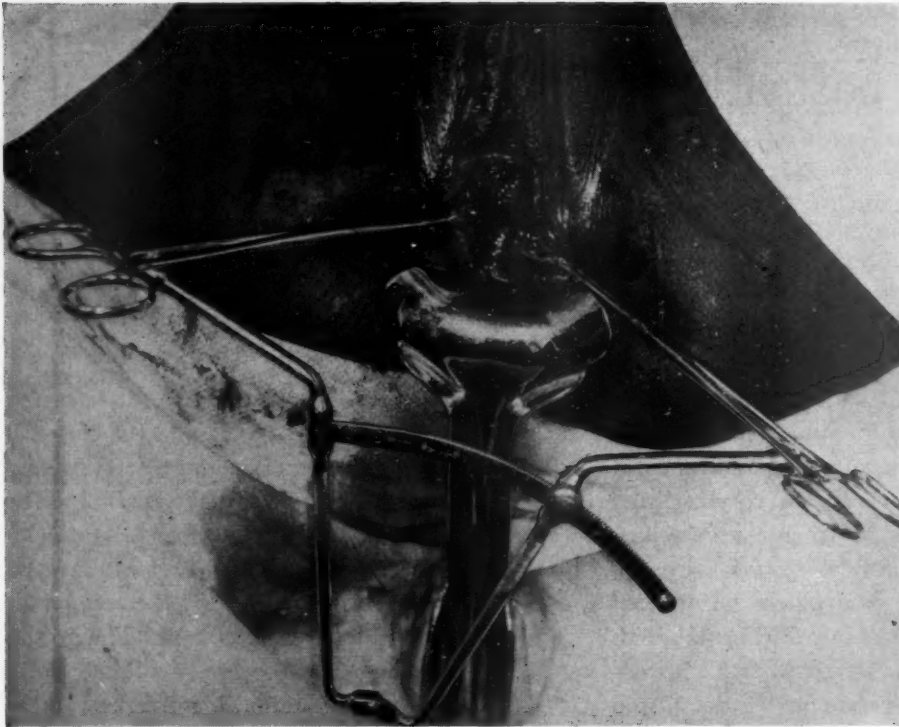


Fig. 2. Cervical Twin Ring Retractor attached to postpartum cervix (primipara).

of the Retractor as the slight pull of gravity and the surrounding vaginal vestibule serves to fix the cervix well enough for suturing. If there has been an episiotomy or perineal laceration it is best to suture the cervix first

since the cervix is pulled down more easily immediately after delivery.

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Pathogenesis of ABO hemolytic disease

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FOLLOWING the discovery of the ABO blood groups by Karl Landsteiner^{1, 2} at the turn of the century, the idea suggested itself that an incompatibility between the mother and fetus in utero might have a harmful effect on the mother and the fetus. As early as 1905, Dienst³ suggested that accidental transfusion of incompatible fetal blood into the maternal circulation might be the cause of toxemia of pregnancy. However, Dienst himself abandoned the hypothesis when studies on additional cases showed that toxemia could occur also when blood groups of mother and fetus are compatible. Other investigators⁴ suggested that blood group incompatibility with respect to the ABO groups might be a cause of icterus in the newborn. This hypothesis was also abandoned when it was found that the most severe cases occurred when the ABO blood group of the fetus was compatible with that of the mother. Still other investigators, notably Hirszfeld,⁵ attempted to show differences in birth weight and other traits between babies born of homospecific preg-

nancies and babies from heterospecific pregnancies. This line of investigation was also discontinued when studies on larger series of cases failed to support the hypothesis.⁶

With the discovery of the Rh factor⁷ and the demonstration of the role of Rh sensitization in the pathogenesis of erythroblastosis fetalis,⁸ interest in the subject was revived. While the bulk of the cases of erythroblastosis could be traced to Rh sensitization of the mother, there were many in which the disease occurred even though the mother was Rh positive. Some of these atypical cases were explained by the discovery of the other blood factors besides the factor **Rh₀** of the Rh-Hr system.^{9, 10} Of these, factor **hr'** has proved to be the most common cause, after **Rh₀**, of isosensitization in pregnancy.^{11, 12} Examples have also been encountered of sensitization to other Rh-Hr factors such as **rh'**, **rh''**, **rh^v**, **hr''** etc., as well as to factors of other blood group systems such as factors **S** and **Kell**.¹³ These observations stimulated interest once more in the possibility that sensitization to the A and B agglutinogens might give rise to hemolytic disease of the newborn.

In 1944, Halbrecht¹⁴ described a clinical entity which he designated as icterus praecox. The babies affected with this syndrome exhibited early neonatal jaundice, at times associated with a mild anemia, from which recovery almost invariably occurred without treatment. Thus, this syndrome, in some respects, resembled physiological icterus, except for the earlier onset of the

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jaundice and the frequently associated anemia. In 57 (or 95 per cent) of 60 such cases studied by Halbrecht, the pregnancies proved to be heterospecific, i.e., the red cells of the baby had an agglutinin A or B incompatible with the serum of the mother. On the other hand, in a parallel series of 2,000 normal maternity cases, only 26.5 per cent of the pregnancies were heterospecific. This established beyond reasonable doubt that the syndrome designated *icterus praecox* was due to ABO incompatibility. Thus, the cases studied by Halbrecht were mild examples of what is now designated ABO hemolytic disease.

Other investigators, notably Polayes,¹⁵⁻¹⁸ reported cases of erythroblastosis fetalis due to ABO sensitization which were clinically severe, resembling those caused by Rh sensitization.^{19, 20, 21, 22} Polayes and Wiener carried out titrations on the serums of the mothers of the affected babies and showed that the alpha and beta antibody titers were strikingly higher than in heterospecific pregnancies in which the baby was not affected.

However, many workers in the field were skeptical, at first, about the existence of the entity, ABO hemolytic disease. In 1944, one of us (A. S. W.) studied a series of cases of neonatal jaundice and anemia which could not be explained on the basis of Rh sensitization. In 40 such families, there were 34, or 85 per cent, in which an ABO incompatibility was present. Since, as already mentioned, only about 25 per cent of normal pregnancies are heterospecific, this indicated that more than half of the cases were probably due to the ABO incompatibility. The validity of this interpretation was established by titration of the maternal alpha and beta antibodies by the plasma conglutination as well as the saline agglutination techniques. Yet, despite the earlier publications of Halbrecht and Polayes, the observations were greeted with such skepticism that two leading journals refused to publish this article, which was then printed privately in pamphlet form.²²

Since 1946, many articles and monographs^{23, 24} have been published on ABO

hemolytic disease, which, though elaborate, throw little or no light on the pathogenesis. This syndrome differs in certain respects from Rh hemolytic disease and poses a number of as yet unanswered questions. In Rh hemolytic disease, the first-born Rh-positive baby usually escapes, because the Rh-negative mother must first be sensitized to the Rh factor. Unless a mother has been sensitized to the Rh factor by an injection of Rh-positive blood, sensitization can occur only if some of the fetus's Rh-positive red cells traverse the placental barrier, either during pregnancy or during delivery. In the case of ABO hemolytic disease, on the other hand, the first-born incompatible baby is often affected. This has been explained, in part, by the observation that, except during the first months of life, those alpha and beta isoantibodies which do not react with the individual's own red cells are regularly present in the serum (Landsteiner's rule). To account for the observation that ABO hemolytic disease results from only a small percentage of heterospecific pregnancies, the explanation has been invoked that the antibodies are harmless to the fetus unless present in the mother's serum in high titer. However, it has been difficult to draw a definite line between a safe and a dangerous titer, although there does appear to be some correlation between maternal antibody titer and the severity of the manifestations in the baby.²⁵

The available evidence indicates that the Rh-Hr substances are restricted to the red cells. On the other hand, the ABO blood group substances are present not only in the red cells but also in organ cells, and, in 80 per cent of individuals, known as secretors, they are present as well in water-soluble form in the secretions and body fluids.^{6, 26} This suggests the question of whether the secretor status of the fetus plays any role in the pathogenesis of the disease.

Observations regarding ABO hemolytic disease that require explanation are the weak or negative reactions of the affected baby's red cells in the direct antiglobulin

test and the finding that, with few exceptions, the disease occurs only when the mother belongs to Group O.²⁷

During the past 15 years we have had occasion to study many families in which ABO hemolytic disease occurred. The purpose of this report is to present our observations in these families in an attempt to throw light on the pathogenesis of this clinical entity.

Materials and methods

The families which make up the present study came to our attention in one of two ways. In some cases, a newborn baby unexpectedly developed jaundice and/or anemia and one of us was called in consultation. In other cases, the expectant mother was referred to us for study because she previously had had a baby with hemolytic disease and the obstetrician wished to know whether the expected child would also be affected.

In all cases, blood was taken from the affected child and all siblings that were available, as well as from the parents. These specimens were tested for their ABO groups and subgroups, as well as for their Rh-Hr types. In most cases the Kell type was also determined. The M-N types were routinely determined, but are not reported in this study except to mention that in no case did the results of those tests exclude paternity or maternity. At the same time that the blood specimens were obtained, saliva specimens were also collected whenever possible. These were heated in a boiling water bath for 10 minutes in order to destroy any blood group enzyme that might be present and then stored in the refrigerator until tested for their content of A, B, and H substances.

The serum of the mother, and at times also that of the affected baby, was titrated to determine the content of isoantibodies. For these titrations, suspensions of red cells of Groups A₁, A₂, and B were used, while Group O cells were included as a negative control. All titrations were carried out by the saline agglutination and the acacia con-

glutination method, except for a few families, earlier in the study, where the plasma conglutination method was used instead of the acacia method. These techniques have been described in detail elsewhere.²⁵ In this connection, it is important to emphasize the relatively poor reproducibility of all serological titrations. Such titrations are carried out with a series of doubled dilutions of serum, and even under ideal conditions, differences of the order of one or two tubes (100 per cent to 200 per cent) are the rule.⁶ The titers are affected by the freshness of the test cells, temperature, period of incubation, and manner of handling the tubes when the end point is read, so that, in practice, titrations on one and the same serum carried out at different times may exhibit variations in titer values as high as 4 serum dilutions (800 per cent). Such results may at times give the illusion of a rising or falling antibody titer. Ideally, therefore, the serum samples should be stored in the freezer, so that when titrations are repeated at a later date the new blood sample can be titrated in parallel with the old one. When this is done, it is often found that what at first appeared to be a change in titer was in reality caused by limitations of the titration technique. Unfortunately, in the present study, it was not always practicable to carry out such parallel titrations, and this probably accounts for some of the variations in antibody titer which were encountered from time to time.

All Group A blood specimens were tested with anti-A₁ serum to determine the subgroup. As is well known, this test does not give reliable results on blood samples from newborn babies,^{6, 55} so whenever possible the tests were repeated when the baby was older. When this could not be done, the group of the baby was recorded without specifying the subgroup.

All saliva specimens were tested for their capacity to inhibit anti-A and anti-B serums, and anti-H lectin (*Ulex europaeus*) by the quantitative inhibition technique.²⁸ As controls, parallel titrations were carried out with commercial preparations of blood

Table I. List of cases

Case number	Father	Mother*	Pregnancies		Year	Maternal isoagglutinin titers								Clinical data§
			Infant's blood type	Clinical data†		Time of test‡	Saline			Acacia				
							A ₁	A ₂	B	A ₁	A ₂	B		
1	A ₁ , Rh ₀ , secretor	O, rh, non-secretor	1. A ₁ , rh, secretor	Severe hem. dis. ♀; exch. transf.; recov.; no seq.	1954	At delivery 18 days p.p.	120	60	30	1,600	480	30	17 hr.—when first seen I.I. = 80 u.; after exch., maximum I.I. = 96 u.	
			2. —	Misc.	1956									
			3. A, Rh ₀ , secretor	Severe hem. dis. ♂; exch. transf.; recov.; no seq.	1957	At delivery 15 days p.p.	120	60	15	1,500	1,500	140	Cord I.I. 36 u.; before exch. transf., I.I. = 130 u.; after exch., maximum I.I. = 84 u.	
2	B, Rh ₀ , rh, secretor	O, Rh ₀ , Rh ₀ , secretor	4. O, rh	Normal	1958	During pregnancy	115	55	260	680	530	1,300	Average of 3 titrations	
			1. B, Rh ₀ , Rh ₀ , secretor	Normal ♂	1955									
			2. Twins a. B ₀ , Rh ₀ , Rh ₀ , secretor b. O, Rh ₀ , Rh ₀ , secretor	Severe hem. dis. ♂; exch. transf.; recov.; no seq.	1957	At delivery 18 days p.p.	10	1	40	50	15	1,500	When first seen I.I. = 84 u.; after exch. transf., I.I. 30 u.	
3	A ₁ , Rh ₀ , rh, secretor	O, Rh ₀ , rh, non-secretor	1. A ₁ , rh, secretor	Normal ♀	1947									
			2. —	Died 13 hours; cerebral hemorrhage	1951									
			3. A ₁ , rh, non-secretor	Hem. dis. ♀; transf. washed RBC; recov.; no seq.	1952	8 days p.p.	500	—	128	1,000	—	500	Baby had bloody diarrhea	

4 B, Rho, secretor		O, Rh, Rh ₀ , secretor	1. B, Rh ₀ , rh, secretor	Hem. dis. ♀; simple trans.; recov.; no seq.	1949	2 days p.p.	6	—	6	11	—	96
			2. —	Spont. ab.								
			3. B, Rh ₀ , rh, secretor	Severe hem. dis. ♂; exch. trans.; recov.; no seq.	1943	9th mo. preg.	18	—	70	60	—	640 When first seen I.I. = 80 u.; after exch. transf., I.I. = 40 u.
5 B, Rho, secretor		O, rh, secretor	1. B, Rh ₀ , secretor	Normal ♀	1946							
			2. B, Rh ₀ , secretor	Severe hem. dis. ♂; exch. transf.; recov.; no seq.	1947	3rd mo. preg.	150	—	4,000	100	—	6,400 Cord I.I. = 40 u.; pretransf., I.I. = 64 u.; posttransf., I.I. = 24 u.
						4th mo. preg.	30	—	1,800	60	—	1,800
						5th mo. preg.	48	—	4,000	48	—	1,000
						6th mo. preg.	60	—	1,920	50	—	4,000
						8th mo. preg.	96	—	2,000	80	—	2,000
						9th mo. preg.	40	—	1,600	30	—	1,600
						At delivery	40	—	1,600	120	—	3,200
							160	—	2,500	480	240	5,000
6 B, Rh, Rh ₀ , secretor		O, Rh, rh, secretor	1. B, Rh ₀ , rh, secretor	Hem. dis. ♀; exch. transf.; recov.; no seq.	1954							Not treated by authors
			2. —	Spont. ab.								
			3. O, Rh positive	Between 2nd and 3rd pregnancies Normal ♂	1956	Interval titers	60	20	240	160	80	1,920
					1957	2nd mo. preg.	80	60	240	320	160	960
						6th mo. preg.	60	10	160	480	60	600
						8th mo. preg.	40	20	30	60	30	400
					1955		25	20	120	320	30	1,500
7 A, Rh, Rh ₀ , secretor		O, rh, secretor	1. A, rh, secretor	Hem. dis. ♀; 2 exch. transf.; recov.; no seq.	1957	22 mo. p.p.	30	10	10	240	40	60
8 B, Rh, Rh ₀ , secretor		O, rh, secretor	1. O, rh, non-secretor	Normal ♀	1950							Not treated by authors
			2. —	6 mo. S.B.	1952							
			3. B, Rh ₀ , rh, secretor	Hem. dis. (?) ♂	1953							Said to have been anemic after birth; alive and well
			4. —	9 mo. S.B.	1954							
			5. O, Rh ₀ , rh, non-secretor	Normal ♂								

Titer reported to be 1,024

Not treated by authors

Said to have been anemic after birth; alive and well

Table I.—Continued

Case number	Father	Mother*	Pregnancies		Year	Maternal isoagglutinin titers						Clinical data§	
			Infant's blood type	Clinical data†		Time of test‡		Saline		Acacia			
						A ₁	A ₂	B	A ₁	A ₂	B		
6	B, Rh ₁ -rh, non-secretor		Severe hem. dis. ♀; treated with cortisone and A and B group subst.; recov.; no follow-up	1956	2 days p.p. 20 days p.p.	120	30	60	480	320	400	Not treated by authors; Cord bilirubin = 5 mg.; at 39 hr. bilirubin = 35 mg.; at 45 hr. bilirubin = 41 mg.; at 83 hr. bilirubin = 24.5 mg.; at 120 hr. bilirubin = 7.3 mg.	
						60	20	20	800	440	240		
7	B, Rh ₁ -rh, secretor		Severe hem. dis. ♀; exch. transf.; recov.	1958	1 day p.p.	80	50	30	960	400	160	Not treated by authors; pretransf. bilirubin = 18 mg.; posttransf. bilirubin = 10.5 mg.	
9	A ₁ B, Rh ₁ rh, secretor	O, Rh ₂ rh, secretor	1. B, Rh ₀ , secretor	1946									
			2. B, Rh ₁ -rh			Hem. dis. ♂; untreated; cerebral palsy; died							
			3. B, Rh ₀ , secretor			Severe hem. dis. ♀; exch. transf.; recov.; no seq.	40	—	60	160	—		960
10	A ₁ B, Rh ₂ rh, secretor	O, rh, non-secretor	1. —	1950	9th mo. preg. 11 days p.p.	40	—	60	160	—	960		
			2. —			Spont. ab.	120	—	120	160	—		1,280
			3. A ₁ , Rh ₂ , secretor			Hem. dis. ♂; exch. transf.; recov.; no seq.	40	40	20	1,920	640		160
11	A ₁ , Rh ₁ rh, secretor	O, Rh ₁ Rh ₁ , secretor	4. A ₁ , Rh ₂ , secretor	1956	3 mo. p.p.	60	60	20	800	400	80	Cord I.I. = 24 u.; at 24 hr. I.I. = 48 u.; at 36 hr. I.I. = 66 u.	
			5. B			Mild hem. dis.; untreated; no seq.	80	50	25	960	480		120
			1. O, Rh ₁ -rh, secretor			Normal ♂	30	20	15	1,000	500		100
12	A ₁ , Rh ₁ rh, secretor	O, Rh ₁ Rh ₁ , secretor	2. A ₁ , Rh ₂ , secretor	1957	4th mo. preg. 5th mo. preg. 6th mo. preg. 7th mo. preg. 9th mo. preg.	60	60	20	800	400	80		
			3. A ₁ , Rh ₂ , secretor			Hem. dis. ♂; exch. transf.; recov.; no seq.	80	50	25	960	480		120
			4. A ₁ , Rh ₂ , secretor			Hem. dis. ♂; exch. transf.; recov.; no seq.	30	20	15	1,000	500		100
13	A ₁ , Rh ₁ rh, secretor	O, Rh ₁ Rh ₁ , secretor	5. B	1958	4th mo. preg. 5th mo. preg. 6th mo. preg. 7th mo. preg. 9th mo. preg.	22	15	20	320	320	240		
			1. O, Rh ₁ -rh, secretor			Normal ♂	30	20	15	480	280		90
			2. A ₁ , Rh ₂ , secretor			Hem. dis. ♂; exch. transf.; recov.; no seq.	30	20	15	480	280		90

secretor	secretor	rh, secre- tor	2. A, Rh _i - rh, secre- tor	Hem. dis. ♀; un- treated; recov.; no seq.	1957	48 hr. p.p. 17 days p.p.	10	10	60	60	60	200	At 48 hr. I.I. = 108 u.; postpartum rise in titer
12 A, Rh _s , secretor	O, Rh _i rh, secretor		1. A _i , Rh _i - Rh _s , secretor	Hem. dis. ♂; un- treated; recov.; no seq.	1957	6 days p.p. 1 mo. p.p.	5	8	15	120	120	30	At 48 hr. I.I. = 108 u.; at 72 hr. I.I. = 112 u.; postpartum rise in titer
13 A _i , Rh _i rh, secretor	O, Rh _s , secretor		1. A _i , Rh _s , secretor	Normal ♂									Cesarean delivery
			2. A _i , rh, secretor	Mild hem. dis. ♂; untreated; recov.; no seq.	1957	10 days p.p.	120	60	10	1,500	750	60	Cesarean delivery; not treated by authors; 5th day, I.I. = 72 units
14 A _i , Rh _i rh, secretor	O, Rh _i Rh _i , non- secretor		1. ———	Spont. ab., 2 mo.	1945								
			2. ———	6 mo. S.B.	1954								
			3. ———	6 mo. S.B.	1956								
			4. A, Rh pos.	5½ mo. S.B.	1956	2 mo. p.p.	160	80	15	1,600	800	20	
15 B, Rh _i rh, secretor	O, Rh _i rh, secretor		1. O, Rh _i - rh, secre- tor	Normal ♂	1946								
			2. B, Rh _i - Rh _s , secretor	Normal ♂	1948								
			3. B, Rh pos.	Hem. dis. ♂; un- treated; cerebral palsy									Premature; not seen by authors
			4. B, Rh _i - rh, secre- tor	Hem. dis. ♀; exch. transf.; recov.; no seq.	1954	2nd mo. preg.	15	—	35	200	—	1,600	Baby not treated by authors
16 A _i B, Rh _i rh, secretor	O, Rh _s , secretor		1. A _i , Rh _i - rh, secre- tor	Normal ♀	1950	3 yr. p.p.	30	15	60	200	120	1,000	
			2. B, Rh _s , secretor	Normal ♂	1952								
			3. A _i , Rh _s , non- secretor	Hem. dis. ♀; treat. expect- antly; mentally retarded	1955	2 yr. p.p.	70	40	60	320	160	480	Baby not treated by authors

2. A ₁ , Rh ₁ -Rh ₂		Hem. dis. ♀; untreated; recov.; no seq.	1957	7 days p.p.	8 320	20 80	0	240 800	160 500	0	7th day I.I. = 84 u.		
21	A ₁ , rh, secretor	O, Rh ₁ rh, secretor	1. A ₁ , Rh ₁ -rh, secretor	Hem. dis. ♀; untreated; recov.; no seq.	1950	Jaundiced first week of life							
			2. A ₁ , Rh ₁ -rh, secretor	Hem. dis. ♂; untreated; recov.; no seq.	1955	3 days p.p.	64	40	15	1,280	640	30	At 72 hr. I.I. = 120 u.; at 96 hr. I.I. = 120 u.
22	A ₁ , Rh ₁ Rh ₂ , secretor	O, Rh ₁ rh, secretor	1. A ₁ , Rh ₁ -Rh ₁ , secretor	Normal ♀	1958	2 years p.p.	80	160	40	3,500	3,500	140	Cesarean delivery
			2. A ₁ , Rh ₁ -Rh ₂ , secretor	Mild hem. dis. ♂; untreated; recov.	1955	At term	15	12	5	880	800	5	Cesarean delivery
23	A ₂ , Rh ₁ Rh ₂ , secretor	O, Rh ₁ rh, secretor	1. A ₂ , rh, secretor	Normal ♂									
			2. O, Rh ₁ -Rh ₁ , secretor	Normal ♀									
			3. A ₂ , Rh ₂ -Rh ₁ , secretor	Hem. dis. ♂; transf. packed cells; recov.	1955	2 days p.p.	240	120	40	800	240	160	I.I. = 96 u.
24	A ₁ , Rh ₁ rh, secretor	O, rh, secretor	1. O, rh	Normal ♂									
			2. ——— non-secretor	Neonatal death									
			3. O, Rh ₂ , secretor	Normal ♀									
			4. A ₁ , rh, secretor	Hem. dis. ♂; exch. transf. at 28 hr.; recov.	1955	2 days p.p.	3	3	2	512	256	80	Cesarean delivery; pre-exch. transf., I.I. = 56 u.; postexch. transf., I.I. = 24 u.; at 95 hr. I.I. = 108 u.
25	A ₁ B, Rh ₁ -Rh ₁ , secretor	O, Rh ₁ Rh ₁ , secretor	1. B, Rh ₁ -Rh ₁ , secretor	Normal ♂	1951								
			2. B, Rh ₁ -Rh ₁	Mild hem. dis. ♂; untreated; recov.; no seq.	1956	2 days p.p.	20	10	15	200	100	100	Abruptio placentae; cesarean section 6 weeks premature; peak I.I. = 60 u.
					1958	18 mo. p.p.	20	10	80	400	320	960	

Table I.—Continued

Case number	Father	Mother*	Pregnancies		Year	Maternal isoagglutinin titers										Clinical data§
			Infant's blood type	Clinical data†		Time of test‡	Saline			Acacia						
							A ₁	A ₂	B	A ₁	A ₂	B				
26	A ₁ , Rh ₁ rh, non-secretor	O, Rh ₁ Rh ₁ , secretor	1. A ₁ , Rh ₁ -Rh ₁ , secretor	Mild hem. dis. ♂; untreated; recov.; no seq.	1957	3 days p.p.	20	8	40	480	320	480				
27	A ₁ , Rh ₂ secretor	O, Rh ₁ Rh ₁ , non-secretor	1. A ₁ , Rh ₁ -rh, secretor	Normal ♀	1951											
			2. O, Rh ₁ -Rh ₂ , secretor	Normal ♂	1954											
28	A ₁ , Rh ₁ rh, secretor	O, Rh ₁ rh, secretor	3. A ₁ , Rh ₁ -Rh ₂ , secretor	Mild hem. dis. ♀; untreated; recov.; no seq.	1957	4 days p.p. 2 mo. p.p.	5 15	5 15	5 10	150 160	150 80	150 100	At 4 days I.I. = 40 u.; neonatal anemia			
			1. —	Mongoloid ♀; died at 4 mo.	1942											
			2. A ₁ , Rh ₁ -rh, secretor	Hem. dis. ♂; 2 simple transf.; cerebral palsy	1943											
29	A ₁ , rh, secretor	O, Rh ₂ , non-secretor	3. A ₁ , Rh ₁ -rh, secretor	Hem. dis. ♀; recov.; no seq.	1950	2nd mo. preg. 5th mo. preg. 7th mo. preg.	70 30 75	— — —	70 30 160	140 80 320	— — —	240 110 800	Cord I.I. = 24 u. Jaundice cleared after 48 hr.			
					1951											
			4. O, Rh ₁ -rh	Normal	1957											
			1. O, Rh ₂ , secretor	Normal ♀	1952											
			2. O, Rh ₂ , non-secretor	Normal ♂	1953											
			3. —	Spont. ab. 6 weeks Hem. dis. ♂; simple transf.; recov.; no seq.	1954											
			4. A ₁ , rh, secretor		1955											
															Not treated by authors	

Not treated by authors

Not treated by authors

Cord bilirubin 5 mg. %;

1956

Hem. dis. ♂;

5. A₁, Rh₂, secretor

[illegible]

Table I.—Continued

Case number	Father	Mother*	Pregnancies		Year	Maternal isoagglutinin titers						Clinical data§		
			Infant's blood type	Clinical data†		Time of test‡	Saline			Acacia				
							A ₁	A ₂	B	A ₁	A ₂		B	
35	A ₁ , Rh ₁ , Rh ₂ , non-secretor	O, Rh ₂ rh	1. A ₁ , Rh ₁ -rh, secretor	Ment. retarded ♂	1946								No neonatal jaundice	
			2. A ₁ , Rh ₁ -rh, secretor	Hem. dis. ♂; given 4 simple transf.; neurological seq.; interval titer	1948	10 days p.p.	800	—	60	1,600	—	200		Jaundice noted 2nd day, persisted one week; baby not treated by authors
			3. —		1950		—	110	30	—	1,920	400		
					1954		55	30	60	950	900	320		
36	A ₁ , Rh ₁ , Rh ₂ , secretor	O, Rh ₂ rh	1. O, Rh ₂ -Rh ₂	Normal ♂	1943								Baby not treated by authors; deep jaundice 2nd day; jaundice persisted 6 weeks	
			2. O, Rh ₁ -rh	Normal ♀	1945									
			3. A ₁ , Rh ₁ -rh, secretor	Hem. dis. ♀; simple transf.; cerebral palsy	1947									
					1948	6 mo. after 3rd preg.	64	—	16	192	—	80		
37	A ₂ B, Rh ₂ , non-secretor	O, Rh ₂ rh	1. B, Rh ₂ , secretor	Normal ♂	1945								Titrations by plasma method; not acacia	
			2. B, Rh ₂ , secretor	Mild hem. dis. ♂; simple transf.; recov.; no seq.	1948	2 days p.p. 5 days p.p.	64 12	— —	16 22	128 32	— —	128 90		
			3. B, Rh ₂ -rh	Hem. dis. ♂; simple transf.; recov.; no seq.	1950	3rd mo. preg.	20	—	30	70	—	60		
					1951	4 days p.p.	30	—	50	70	—	600		
38	—	O, Rh ₁ rh, non-secretor	1. —	7 mo. S.B.									Peak I.I.-200 u.; opisthotonos	
			2. A ₁ , Rh ₁ -Rh ₂	Hem. dis.; simple transf.; cerebral palsy; died 14 mo.	1952	2 days p.p.	64	30	48	750	500	112		
					1956		40	30	10	600	320	40	Divorced 1st husband, remarried Group O man.	

39	A ₁ , Rh ₁ , Rh ₂ , secretor	O, rh, secretor	1. O, Rh ₁ - rh, secre- tor 2. — 3. — 4. A, Rh ₁ - rh, non- secretor	Normal ♂	1954						Mild neonatal jaundice
				Spont. ab. 3 mo. 1955 Spont. ab. 3 mo. 1956 Mild hem. dis. ♀; 1958 untreated; recov.; no seq.		400	240	30	2,500	2,500	120 Mild neonatal jaun- dice; mild anemia; history of blood loss from cord at birth
40	B, Rh ₁ , Rh ₂ , secretor	O, Rh ₁ , rh, non- secretor	1. B, Rh ₁ - Rh ₁	Hem. dis. ♀; recov.; no follow-up	1958	7 days p.p.	40	10	40	320	160 1,280 Jaundice 2nd day and anemia; I.I. at 7 days = 96 u.; Hgb. 9.5 Gm.
41	B, Rh ₁ , Rh ₂ , secretor	O, Rh ₁ , Rh ₁	1. B, Rh ₁ - Rh ₁ , secretor 2. B, Rh ₁ - Rh ₁ , secretor	Normal ♂ Mild hem. dis. ♀; untreated; recov.; no seq.	1958	1 day p.p.	15	10	60	320	160 2,500 Peak I.I. = 84 u.; No anemia
42	A ₁ , Rh ₁ , rh, secretor	O, rh, secretor	1. O, rh, secretor 2. A ₁ , rh, secretor	Normal ♂ Mild hem. dis. ♂; untreated; recov.; no seq.	1954	1 day p.p.	15	5	20	220	80 240 Cesarean delivery; jaundice noted at 24 hours; no anemia
43	A ₁ , Rh ₁ , Rh ₂ , non- secretor	O, Rh ₁ , rh, secretor	1. O, Rh ₁ - Rh ₁ , secretor 2. O, Rh ₁ - rh, secre- tor 3. A ₁ , Rh ₁ - rh, secre- tor	Normal ♀ Normal ♂ Mild hem. dis. ♀; untreated; no seq.	1955	1 day p.p.	50	—	20	600	— 100 Jaundice noted at 12 hours
44	A ₁ , Rh ₁ , Rh ₂ , secretor	O, Rh ₁ , Rh ₂ , secretor	1. A, Rh ₁ - Rh ₁ , secretor 2. — 3. A ₁ , Rh ₁ - Rh ₂ , secretor 4. A ₁ , Rh ₁ - Rh ₁ , secretor	Hem. dis. ♂; untreated; recov.; no seq. Spont. ab. 2½ mo. 1947 Hem. dis. ♀; un- treated; recov.; no seq. Hem. dis. ♂; untreated; recov.; no seq.	1947 1947 1948 1950						Jaundice first 3 weeks of life. Jaundice 10 to 12 days Jaundice 3 or 4 days

Table I.—Continued

Case number	Father	Mother*	Pregnancies		Year	Maternal isoagglutinin titers						Clinical data§	
			Infant's blood type	Clinical data†		Time of test‡	Saline			Acacia			
							A ₁	A ₂	B	A ₁	A ₂		B
44—													
Cont'd													
			5. A ₁ , Rh _i -Rh _i , secretor	Normal ♂	1952								
			6. A ₁ , Rh _i -Rh _i , secretor	Hem. dis. ♀; untreated; recov.; no seq.	1953								Jaundice 2 weeks
			7. A ₁ , Rh _i -Rh _i , secretor	Severe hem. dis. ♂; exch. transf.; recov.; no seq.	1956								
			8. ———	Spont. ab. 6 wk.	1957 1958	1 yr. after 8th preg.	15	—	10	1,600	—	400	
45	A ₁ , rh'rh, secretor	O, Rh _i rh, non-secretor	1. A ₁ , rh, secretor	Normal ♀	1952								
			2. A ₁ , Rh _i -rh', secretor	Severe hem. dis. ♀; exch. transf.; recov.; no seq.	1956	At delivery	640	320	40	2,560	2,560	2,240	Premature, 7 months; birth weight, 4 lbs. 11 ounces; peak I.I. = 108 u.
46	B, Rh _i Rh ₂ , secretor	O, rh, secretor	1. B, Rh pos., secretor	Normal ♀	1954								
			2. B, Rh _i -rh, secretor	Mild hem. dis. ♂; untreated; recov.; no seq.	1956	At delivery 21 days p.p.	25 40	8 40	80 480	60 400	20 200	320 2,000	Jaundiced within 24 hours; cleared in one week; Hgb. = 21 Gm.
47	A ₁ , Rh _i rh, secretor	O, Rh _i rh	1. ———	Mild hem. dis.; untreated; recov.; no seq.	1953								
			2. A, rh, secretor	Mild hem. dis.; untreated; recov.; no seq.	1956	At term	10	5	30	1,250	600	80	Hgb. = 19 Gm.; peak I.I. = 90 u.
48	A ₁ , Rh ₁ ^w -Rh _i , secretor	O, Rh _i rh	1. O, Rh _i -Rh	Mild jaundice ♀; cleared spont. on 8th day	1953	At term	25	—	8	1,280	—	70	Not treated by authors
			2. A ₁ , Rh _i -rh, secretor	Mild hem. dis. ♀; simple transf.; recov.; no seq.	1953	At term							

rh, secre-
tor
simple transf.;
recov.; no seq.

3. ———		Mild hem. dis.; simple transf.; recov.	1954 1955	2nd mo. preg. 7th mo. preg. 8th mo. preg. 9th mo. preg.	80 120 60 120	20 120 30 60	15 20 20 35	500 5,000 2,500 —	250 2,500 1,250 —	44 240 200 —	Anemia, no jaundice		
49	A ₁ , Rh ₀ , secretor	O, Rh ₁ rh, non- secretor	1. A ₁ , rh, secretor	1948	Normal ♀						Not treated by authors		
			2. A ₁ , Rh ₁ - rh, secre- tor	1953	Hem. dis. ♀; exch. transf.; recov.; no seq.								
			3. A ₁ , Rh ₀	1954	Hem. dis. ♂; exch. transf.; recov.; no seq.	60	50	60	1,280	640		80	Not treated by authors
50	A ₁ , rh	O, rh, secretor	1. A ₁ , rh, secretor	1952	Normal ♀						Not treated by authors		
			2. A ₁ , rh, secretor	1954	Normal ♂								
			3. A ₁ , rh, non- secretor	1958	Hem. dis. ♂; un- treated; recov.; no follow-up	40	40	15	640	640		100	Jaundice 5th day, cleared on 14th day
51	A ₁ , Rh ₁ Rh ₁ , non- secretor	O, Rh ₁ Rh ₁ , non- secretor	1. A ₁ , Rh ₁ - Rh ₁ , non- secretor	1949	Hem. dis. ♀; simple transf. (4 times); recov.; no seq.						Not treated by authors		
			2. A ₁ , Rh ₁ - Rh ₁ , non- secretor	1951 1954	Hem. dis. ♀; simple transf. (3 times); cerebral palsy	20	—	20	640	—		200	
			3. A ₁ , Rh ₁ - Rh ₁	1955	Hem. dis. ♀; un- treated; retarded	60	40	80	1,280	400		240	Premature; birth weight, 3 pounds, 15 ounces; no ane- mia; peak I.I.-140 u.
			4. A ₁ , Rh ₁ - Rh ₁ , non- secretor	1956	Hem. dis. ♂; exch. transf.; recov.; no seq.	60	40	40	1,280	1,000		120	Cord I.I. = 36 u.; pre-exch. I.I. = 48 u.

*As explained under Materials and Methods, all type rh mothers were tested for Rh₀ antibodies, but were found not to be sensitized.
†Hem. dis. = hemolytic disease; exch. transf. = exchange transfusion; recov. = recovered; misc. = miscarriage; S.B. = stillbirth; spont. ab. = spontaneous abortion; seq. = sequelae.
‡p.p. = postpartum.
§I.I. = icterus index; u = units.
||Titers by plasma agglutination method instead of acacia.

group substances and salivas from known secretors and nonsecretors.

All tests, namely, the grouping and Rh-Hr typing of the red cells, titrations of alpha and beta antibodies, and inhibition tests on saliva, were carried out by the blind technique.²⁹ In this procedure, one person sets up the tests while a different person reads the reactions without knowing the identity of the test tubes he is examining.

To rule out hemolytic disease caused by sensitization to factors other than A and B, the sera of all Rh-negative mothers were tested for Rh₀ antibodies, the sera of type Rh₁Rh₁ mothers for hr' antibodies, and the sera of Kell-negative mothers, whenever possible, for Kell antibodies. In addition, each mother's serum was screened against a random series of Group O cells by both the antiglobulin and proteolytic enzyme technique to detect any other antibodies which might be present.³⁰ In none of the cases reported in this paper were isoantibodies outside of the ABO system found to be present in the maternal serum.

As an objective measure of the degree of jaundice in the baby, we found acetone icterus index determinations most practicable as well as informative, in that they are easy to carry out and are readily reproducible. Since all proteins are precipitated by acetone added to the serum when the determination is carried out, hemolysis does not interfere with the matching of the color of the diluted serum against the potassium dichromate standards. Bilirubin determinations were done only occasionally, and in our hands there was a fairly constant ratio between the two determinations. We have found that, in general, the icterus index is approximately 6 times the bilirubin concentration in milligrams per cent. Thus, the cord serum from a normal infant may have an icterus index up to 16 units, which corresponds to a maximum bilirubin concentration of about 2.5 mg. per cent.

The present series is biased in certain respects. First, it probably includes a high proportion of severely affected infants. The reason for this is that such infants develop

an early, deep jaundice, and therefore are less apt to be overlooked. The more mildly affected babies with minimal jaundice could be incorrectly classified as having so-called physiological jaundice, and as a result a certain number of mild cases of ABO hemolytic disease could have been missed. On the other hand, it probably includes a few cases of so-called "physiological" neonatal hyperbilirubinemia which were diagnosed as ABO hemolytic disease merely because a blood group incompatibility was found to be present. As an example of the difficulty of diagnosis, one baby with clinical evidence indicating erythroblastosis was treated by exchange transfusion; the failure to demonstrate any serological incompatibility was later explained when the infant was found to have toxoplasmosis.²²

Results

In Table I are summarized the findings in a series of 51 families in which ABO hemolytic disease occurred. These cases are arranged more or less at random, since the charts were mostly reviewed in the alphabetical order in which they were arranged in the file. The entries in the table are self-explanatory, but, for the sake of clarity, the first case will be explained in greater detail.

In Case 1, as can be seen from the table, the first baby was treated by exchange transfusion for severe hemolytic disease. The second pregnancy resulted in a miscarriage. The third pregnancy resulted in the birth of a second erythroblastotic baby, also treated by exchange transfusion. Both babies recovered without sequelae. Recently, there has been a fourth pregnancy which yielded a normal Group O baby. In this case, the mother is Rh negative, but Rh sensitization cannot be implicated since the mother had no Rh antibodies in her serum at the time the erythroblastotic babies were born and, in addition, one of the affected babies is Rh negative. On the other hand, the mother is Group O and both of the affected babies are Group A. For the second baby the subgroup of A

is not given because the baby's blood was tested only at the time of birth. However, the subgroup of the second baby is undoubtedly A_1 , since the father is of genotype A_1O , as follows from the fact that the first child is subgroup A_1 and the last child Group O.

Table I also lists the maternal antibody titers for A_1 , A_2 , and B cells and the date when these titrations were carried out. While, with the technique used here, the titers by the acacia method among random Group O individuals rarely exceeds 250 units, the maternal titer in Case 1 at the time the 2 erythroblastotic babies were born ranged between 1,000 and 3,500 units for A_1 cells, and between 500 and 1,500 units for A_2 cells, while the titer for B cells was considerably lower, namely, only 30 to 140 units. This high titer of the maternal serum for Group A cells accounts for the severe manifestations in the 2 babies and confirms the diagnosis of ABO hemolytic disease. As for the saliva tests, while the mother is a nonsecretor, the father and both affected babies are secretors. After these studies were completed the mother again became pregnant. During the fourth pregnancy, not only was an elevated titer for A and B cells found, but also evidence of minimal sensitization to the Rh factor (titer only 3 units for ficinated cells). (This very weak Rh antibody may have been present but overlooked previously, or may have appeared in the serum for the first time after the delivery of the previous baby, who is Rh positive.) Nevertheless, the resulting

baby was normal, and, significantly, the baby proved to be Group O, Rh negative.

ABO groups

Mothers. One of the most striking results shown in Table II is that the mothers of the affected babies are, with but a single exception (Case 20), all Group O. This peculiarity of ABO hemolytic disease was first pointed out by Rosenfield²⁷ in 1953, although it is also noticeable in reports of earlier series of cases, such as the series reported by Wiener, Sonn, and Hurst²² in 1946. Wiener and Unger^{31,32} found the explanation for this phenomenon by comparing the isoantibody titers of the serums of mothers and their newborn babies. They found that the anti-A and anti-B titers of Group O mothers were on the average 4 times as high as the corresponding titers of serums from mothers of Group B and Group A. Moreover, they found that when the acacia titers of mother and babies were compared, on the average, the ratio of maternal to cord blood titer was one fourth as high when the mother belonged to Group O, as when the mother belonged to Group A or Group B. Thus, on the average, babies of Group O mothers acquire approximately 16 times as much isoantibody by placental transfer as babies of Group A or Group B mothers. On this basis, the predominance of Group O mothers in ABO hemolytic disease is readily understandable.

Fathers. As shown in Table II, the distribution of the ABO groups among the fathers is approximately what one might

Table II. ABO blood group distribution among parents and infants in families of Table I

Source of blood	Number in blood group							
	O	A_1	A_2	A^*	B	A_1B	A_2B	Total
Mothers	50	0	0	—	1	0	0	51
Fathers	0	32	1	—	12	4	1	50†
Nonjaundiced babies	22	11	1	—	9	0	0	43
Born before first affected baby	15	10	1	—	9	0	0	35
Born after first affected baby	7	1	0	—	0	0	0	8
Jaundiced babies	1	40	1	12	21	0	0	75

*Subgroup not established.

†One father not grouped.

expect from the distribution in the general population, except for the absence of Group O and the low incidence of subgroup A₂. This is not surprising since babies of Group O mothers and subgroup A₂ fathers would have to be either Group O or subgroup A₂ and could not belong to subgroup A₁. In general, the red cells of newborn babies are less agglutinable than the cells of adults.⁶ This is especially striking in babies of subgroup A₂; therefore, the red cells of these babies would react only weakly with the maternal isoantibodies so that such babies could be expected to be at most only mildly affected.³³

Babies. The babies in the families studied were subdivided into two groups, namely, those showing evidence of hemolytic disease and those apparently not affected (Table II). None of the babies belonged to Group AB, which is to be expected since when either parent is Group O, none of the children can belong to Group AB. Among the total number of pregnancies in this study, there were 74 babies with neonatal jaundice, and all but one of these belonged to Group A or Group B. The exception was a Group O baby, who obviously could not have ABO hemolytic disease and presumably had physiological jaundice, because no other incompatibility was found. Noteworthy is the shortage of affected babies belonging to subgroup A₂. The subgroup of 12 Group A babies could not be determined with certainty; had these babies been retested when they were older, they presumably would have been found to be subgroup A₁.

In striking contrast was the distribution of the ABO groups among the nonjaundiced babies of whom approximately half proved to be Group O (Table II). These findings are even more instructive when these babies are subdivided into 2 classes, namely, those born before and those born after the first affected baby. As can be seen, once an erythroblastotic baby is born normal babies born thereafter are almost all Group O. This corresponds with the experience in families with Rh hemolytic disease where,

once an affected baby is born, the only chance, with rare exceptions, for a subsequent normal child in the same family is by the birth of an Rh-negative baby.

Secretor status

The suggestion has been made that the secretor status of the baby might play an important role in the pathogenesis of ABO hemolytic disease. Levine³⁴ originally suggested that only nonsecretor babies would be affected, since the presence of group substance (in aqueous solution) in the infant's secretions and body fluids might be expected to inhibit the action of the maternal isoantibodies on the baby's red cells. However, Wiener, Wexler, and Hurst²⁵ found in a series of 15 consecutive babies affected with ABO hemolytic disease that all were secretors. This is the opposite of what one would expect according to Levine's hypothesis. In the general population, among Caucasians, as many as 25 per cent of individuals are nonsecretors,⁶ so that in the series of Wiener, Hurst, and Wexler there was a shortage of nonsecretors in comparison to the normal distribution.

The secretor status of the parents and children in the present study is summarized in Table III. Among the Group O mothers,

Table III. Secretor status of parents and children in families of Table I

	Secre- tor	Nonse- cretor	Un- known	Total
Mothers	31	12	8	51
Fathers	41	5	5	51
Normal babies				
Group O	11	4	6	21
Group A or B	23	0	0	23
Jaundiced babies	51	7	17	75

the secretor status was determined in 43 cases and 12 of these mothers proved to be nonsecretors. This is approximately the normal incidence, which suggests that the secretor status of the mother has little if any bearing on the pathogenesis of ABO hemolytic disease. On the other hand, among the 46 fathers, only 5 proved to be non-

secretors, and this is only about half the expected incidence. However, the size of the series is too small to exclude the possibility that this low incidence of nonsecretors might be due to chance. Among the affected babies, 58 were tested for their secretor status and 7 proved to be nonsecretors, which again is approximately half the expected frequency. The distribution of the secretor status among the babies who were not affected was interesting. Among the 15 Group O babies who were tested, there were 4 nonsecretors, which is about equal to the expected incidence. On the other hand, among 23 normal babies not belonging to Group O, there were no nonsecretors.

These findings are of sufficient interest to make it worthwhile to pursue this line of investigation further in a larger series of cases. Any speculation regarding the significance of the findings would be premature. It must first be determined whether or not this unexpected distribution of the secretor type in families with ABO hemolytic disease is maintained in a larger series of cases.

It has been found in studies on isoimmunization of Group O volunteer donors that soluble blood group substances in secretions such as saliva are more potent antigenically than the blood group substances on red cells.^{35, 36} Therefore, it seems evident that a Group O mother is less apt to be further sensitized if her fetus is a nonsecretor.³⁷ This might account for the shortage of nonsecretors among the fathers and children of our families with ABO hemolytic disease. On the other hand, once the mother has become strongly sensitized, it would seem that nonsecretor babies might be at a disadvantage. This could explain why among the nonjaundiced Group A and Group B babies in the families of Table I there were no nonsecretors in contrast to the jaundiced infants of whom one eighth of those tested proved to be nonsecretors.

These concepts receive support when the families are subdivided according to whether the first heterospecific pregnancy yielded a child with ABO hemolytic disease or not.

Among the families in this study there were 19 in which there were one or more normal babies of Group A or Group B before the first affected baby was born. In all 19 families the normal babies born before the affected baby were secretors. This corresponds with the observation made by Freda³⁸ in a previous paper. He states that, when the baby is a secretor, group specific substances can be demonstrated in significant titer in the amniotic fluid and passage of these substances into the maternal circulation could sensitize her. Significantly, in 4 of the families (Cases 3, 8, 16, and 50 of Table I) there was a pattern of first a normal secretor baby of Group A followed by an erythroblastotic, nonsecretor baby of Group A. In 14 families where the first-born baby of a heterospecific group was affected, only one baby proved to be a nonsecretor.

Maternal isoantibodies

It has become routine to test all Rh-negative expectant mothers for Rh sensitization and, if the mother is sensitized, to titrate the antibodies. Because of the relationship between the height and the duration of the Rh antibody titer and the manifestation of the disease in the infant, such titrations are repeated periodically during each pregnancy, making it possible to detect changes in antibody titer during and after the pregnancy. Much less frequently are similar titrations of alpha and beta isoantibodies carried out during pregnancy. Almost all cases of ABO hemolytic disease are diagnosed after birth, and not antenatally, so that the maternal serum is generally not titrated until delivery or during the postpartum period. In the present series of cases antenatal alpha and beta titrations were carried out only under 2 circumstances: (1) where the expectant mother was Rh negative and was being tested for Rh sensitization and it was noticed that there was also an ABO incompatibility between the expectant mother and her husband and (2) in cases where the expectant mother had a history of having had previous

babies with ABO hemolytic disease. That is the reason why in most of the cases of Table I there is no information regarding the alpha and beta titers during the pregnancy. (Such information might, of course, be helpful in determining whether antenatal alpha and beta titrations have any prognostic value.) Despite this limitation, an analysis of the results of the titrations does yield information of interest.

For the purpose of the analysis the *relative* titers of the maternal serum for Group A and Group B cells, respectively, seem to be more significant than the absolute values. Therefore, in Table IV, the cases have been classified according to the ratio of the alpha to the beta titers of the maternal serum. The cases have been subdivided into 2 categories, namely, those in which the baby belonged to Group A, and those where the baby was Group B. As shown in the table, when the baby was Group A, in most cases the maternal serum had a higher titer for A cells than for B cells. When the baby was Group B, on the other hand, in most cases the titer of the maternal serum for B cells was higher. This indicates that antigenic substances from the fetus in utero must have been responsible for the elevated isoantibody titer in the maternal serum in the majority of the cases.³⁹ In approximately one third of the cases in both categories the maternal alpha and beta titers were approximately equal, and these antibodies may have been mainly of heterogenetic immune origin.⁴⁰

Results of the antibody titrations in Case 1 are unusually interesting. As can be seen, the ratios of the alpha to the beta titers

at term in both the first and third pregnancies were very high corresponding to the clinical condition of the babies, both of whom had ABO hemolytic disease and belonged to Group A. During the fourth pregnancy, on the other hand, while the titers were again high, the ratio between them was reversed, the beta titer now having become twice as high as the alpha titer. In this pregnancy, the baby could not have been the source of the stimulation to the rise in beta titer since it later proved to belong to Group O. Therefore, there must have been some heterogenetic stimulus, as occurs regularly in the case of so-called "natural" alpha and beta antibodies.⁴⁰ Thus, a rise in the alpha and beta antibody titers during a pregnancy cannot be regarded as dependable evidence that the fetus belongs to the corresponding incompatible blood group. Similarly, while in our experience a rise in Rh antibody titer occurring during pregnancy of an Rh-negative woman has always been followed by the birth of an Rh-positive baby,⁴¹ the fact that antigens other than the red cells or secretions of the fetus can stimulate a rise in maternal alpha and beta antibody titer precludes the use of such titrations for reliable antenatal prediction of the baby's ABO group or of ABO hemolytic disease in the baby. A technique which could reliably make the distinction between isoimmune and heteroimmune alpha and beta antibodies might be of considerable value in understanding some of the baffling aspects of ABO immunization.

When interpreting the titers, one must bear in mind that Group O serum contains in addition to isoagglutinins anti-A and

Table IV. Analysis of isoantibody titers of Group O mothers having Group A and Group B erythroblastotic babies

Baby's blood group	Number of cases with the indicated ratio of maternal isoantibody titers for Group A and Group B cells, respectively*											
	64:1	32:1	16:1	8:1	4:1	2:1	1:1	1:2	1:4	1:8	1:16	1:32
A	2	3	3	6	10	3	8	0	0	0	0	0
B	0	0	0	0	0	2	3	0	5	3	0	1

*The table is to be interpreted as follows: of the mothers with Group A babies there were 2 whose alpha titer was 64 times as high as the beta titer, 3 with a 32 to 1 ratio of alpha to beta antibody titers, etc.

anti-B a third isoantibody anti-C.⁴² Anti-C is reactive for both agglutinogens, A and B, since both agglutinogens share the blood factor C in addition to having their own appropriate blood factor, A or B, respectively. Many workers in the field, while acknowledging the existence of the third isoagglutinin, avoid using the term "anti-C" and instead refer to a "cross-reacting antibody." This makes it necessary to point out that certain components of anti-A cross-react with sheep blood red cells and certain components of anti-B with rabbit red cells, so that anti-A and anti-B are also "cross-reacting" antibodies. In fact, the nature of antibodies in general is such that *all* antibodies are at the same time specific and cross-reacting.⁴³ Therefore, the term "cross-reacting antibody" is not only redundant but ambiguous. The simple and explicit term "anti-C," which has been in use for half a century,⁶ should be used instead.

The evidence for the presence of anti-C in Group O serum is obtained from immunization and absorption experiments. It is not generally appreciated that anti-C antibody as well as anti-A and anti-B is not homogeneous, since each actually includes a whole spectrum of antibodies of related specificities. Thus, while certain C antibodies react with approximately equal avidity on Group A and Group B cells, others act more strongly on A than on B cells (anti-C_A), and still others act more strongly on B cells than they do on A cells (anti-C_B).⁴⁴ The concept of different kinds of C antibody renders understandable an observation made by one of us (A. S. W.) in 1947, when the baby in Case 5 of Table I was treated. As can be seen, the maternal serum had a very high titer for B cells and a relatively low titer for A cells. Since potent anti-B sera are difficult to obtain, this mother's serum was absorbed with Group A cells in an attempt to produce a strong and specific anti-B reagent. To our disappointment, the Group A cells not only neutralized the activity for Group A cells but also so reduced the titer for Group B cells that the serum could not be used as a

satisfactory anti-B reagent. Apparently the high titer of the mother's serum for B cells was due to the presence of anti-C_B rather than anti-B. These observations have recently been confirmed by Zuelzer and associates,⁴⁵ who instead of the symbols anti-C, anti-C_A, and anti-C_B, used the designations $\alpha\beta$, $\alpha(\beta)$, and $(\alpha)\beta$, respectively.

Obviously Group A and Group B individuals do not form anti-C since their red cells have the blood factor C. If, as Wiener suggests, therefore, the antibody commonly responsible for ABO hemolytic disease is anti-C rather than anti-A or anti-B, this would explain the excess of Group O mothers in families with ABO hemolytic disease. This raises the question of why the C antibody appears to be more dangerous for the baby than anti-A and anti-B. Part of the answer appears to be that all incompatible antibodies are harmful to the baby but the C antibody appears to be formed more readily. The C antibody is an antibody of lower specificity, as indicated by its ability to cross-react with A and B cells. There is evidence that on prolonged immunization not only is more antibody formed, but the antibodies formed tend to become less specific.⁴³ For example, if one desires to prepare anti-human precipitin for medicolegal identification of dried stains of human blood, the immunized rabbits should be bled as soon as possible after the antiserum is of adequate titer. The reason for this is that when the injections are continued, the antisera develop cross reactions for bloods of lower mammals (mammalian reaction). Similarly, on prolonged immunization of Group O individuals, the antibody formed in highest titer would be expected to be of specificity anti-C. Moreover, protracted immunization produces predominantly the univalent form of antibody, and this is the molecular form of antibody that has been found to traverse the placental barrier.^{46, 47}

An important difference between ABO hemolytic disease and Rh hemolytic disease is the manner in which isosensitization can occur. Rh antibodies rarely if ever occur spontaneously in the serum of Rh-negative

individuals. Such antibodies are formed only after exposure of the individual to human red cells containing the Rh antigen.^{30, 48} On the other hand, anti-A and anti-B (and anti-C) are regularly present in conformity with Landsteiner's rule, except during the neonatal period and in individuals with agammaglobulinemia. These so-called "natural" isoagglutinins appear to be the result of inapparent sensitization to A-like and B-like antigens which are ubiquitous in nature.⁴⁰ For example, A-like and B-like antigens have been found in blood of lower animals, in plants, and in certain strains of bacteria, and protozoa, etc.⁶ Therefore, it is inevitable that by ingestion or infection all human beings will become sensitized to A and B antigens. It seems possible if not probable that the isoantibodies produced as a result of heteroimmunization may be of lower specificity than those resulting from isoimmunization in pregnancy. Since antibodies of lower specificity tend to have lower avidity, so-called "natural" isoantibodies might be expected to be less harmful to the baby.

On this basis, Wiener⁴⁹ has suggested that two forms of ABO hemolytic disease might exist. In one form, resulting from high titers of the so-called natural antibodies, the first-born baby of an incompatible blood group would be affected, but the manifestations would tend to be mild. In the second form, where the baby's blood or secretions are the source of the maternal sensitization, the first-born baby of an incompatible blood group would often escape, but in the subsequent affected babies the manifestations would tend to be more severe and to resemble typical Rh hemolytic disease. For example, in Cases 1 and 2 of Table I, the erythroblastotic infants were severely affected. In Case 1 where the affected babies belonged to Group A, the anti-A titer of the maternal serum was as high as 3,500 units, while the titer for B cells never exceeded 140 units. In Case 2, where the affected baby belonged to Group B, the maternal anti-B titer was 1,500 units whereas the titer for A cells was only 50 units. In Case 2, it seems evident that the source of

the maternal isosensitization must have been the first pregnancy since the first baby, though normal, was Group B and a secretor. The second pregnancy in Case 2 resulted in fraternal twins, and significantly the Group B baby was severely erythroblastotic while the Group O baby was normal. In contrast, in Case 42, the first pregnancy resulted in a normal Group O infant and the second pregnancy resulted in a Group A infant with mild hemolytic disease. In this case, the maternal titer for A₁ cells was 220 units and for B cells 240 units. This suggests that the antibody in the serum was predominantly "natural" anti-C. Unfortunately, Table I does not provide convincing evidence either for or against the existence of 2 forms of ABO hemolytic disease, but this may be due to the fact that this series is relatively short and, as is explained in this paper in the section on Materials and Methods, is a biased one in that it consists predominantly of families with severely affected infants.

Comment

At one time it was the practice to inject intramuscularly untyped whole human blood for prophylaxis and treatment of measles, poliomyelitis, and other infections, as well as for its supposed hemostatic effect in newborn babies after traumatic deliveries. It is impossible to tell how many thousands of iatrogenic cases of Rh hemolytic disease can be blamed on this practice, which fortunately was abandoned many years ago. Routine Rh typing of patients and donors before blood transfusions has served to prevent other cases of Rh sensitization in prospective mothers, though, unfortunately, errors in Rh typing continue to occur and are still responsible for a number of cases even at this late date. On the other hand, the opportunities for artificial induction of sensitization to the A and B agglutinogens are manifold because these antigens are not restricted to human red cells but are present also in human body secretions, saliva, urine, and in addition, A-like and B-like antigens are ubiquitous in nature, as has been

pointed out. The transfusion of pooled human plasma,^{50, 51} Group O blood conditioned with A-B blood group substances,⁵² hormones extracted from human urine,⁶⁴ and tetanus antitoxin prepared in horses⁵³ have all been found to stimulate a marked rise in titer of the alpha and beta antibodies. This raises the question as to how many cases of ABO hemolytic disease are iatrogenic in origin. Obviously, physicians should be circumspect about injecting into female patients from birth to menopause any material which might be capable of stimulating a rise in the titer of the alpha and beta isoantibodies.

There is much discussion in the literature regarding methods for distinguishing between so-called natural and immune alpha and beta antibodies in the serum of Group O mothers for the purpose of diagnosing ABO hemolytic disease in their babies. Such discussions are based on a misconception since all alpha and beta antibodies are of immune origin. However, as has been pointed out by Wiener⁴⁰ and again in this paper, alpha and beta antibodies can be of heteroimmune as well as of isoimmune origin. As has been pointed out, A-like and B-like antigens are ubiquitous in nature so that early in life contact with such antigens is inevitable. This would account for the regular occurrence of the so-called "natural" isoagglutinins in conformity with Landsteiner's rule. Because of their heteroimmune origin the so-called "natural" isoagglutinins react with human red cells with greater intensity at low temperatures than at body temperature. Isoimmune alpha and beta isoantibodies on the other hand act with greater avidity and titer at body temperature than at refrigerator temperature.²⁵ Unfortunately, the difference in the in vitro behavior of heteroimmune and isoimmune alpha and beta antibody is not sharp enough to use this as a method of differentiating them. At any rate, it seems that a very important factor is the quantity of antibody present in the maternal serum. If the maternal antibodies are of high enough titer, whether heteroimmune or isoimmune,

the baby is apt to be affected if his blood group is incompatible. However, as in Rh hemolytic disease, the correlation between antibody titer and severity of the disease is by no means absolute.

In ABO hemolytic disease the antiglobulin test on the affected baby's red cells is almost always negative or at best weakly positive. This is in contrast to Rh hemolytic disease where the direct antiglobulin test is almost always positive.⁵⁴ The explanation for this can perhaps be found in the fact that A and B blood group substances, unlike the Rh substance, are not restricted to the red cells. Presumably, as the maternal alpha and beta antibodies pass into the fetal circulation by traversing the placenta, they combine with A and B blood group substances present in solution in the body fluids, leaving only a fraction of the antibody molecules free to combine with the red cells. Moreover, the combination of antibody with red cells is not a firm one, especially since the A and B agglutinogens of the fetus are not completely developed (as shown by the lower avidity of the agglutination reaction of such cells in the in vitro tests). Antibodies eluted from the red cell in vivo may be partially or completely neutralized before they are able to react with the red cells again. In the case of Rh hemolytic disease, on the other hand, the combination between antibody and red cell antigen is firmer and elution from the red cell does not occur as readily. Also, there is no competition for the antibody molecules from Rh antigen in solution. In the in vitro tests, the baby's red cells must be washed 3 or 4 times with saline solution before the antiglobulin reagent is added. In ABO sensitization, the washing may serve to elute the antibody, so in such cases the direct agglutination test in plasma or acacia may be preferable.^{56, 57, 65}

Failure to recognize the existence of 2 forms of ABO hemolytic disease has led to certain misconceptions regarding the management. Since the milder form of the disease (icterus praecox) is by far more common, this has led to the incorrect impres-

sion that ABO hemolytic disease is a benign disorder that should be treated expectantly. However, as Polayes¹⁵⁻¹⁸ was the first to demonstrate, ABO hemolytic disease can be as severe as typical Rh hemolytic disease. Moreover, Wiener and Brody²⁰ described a case involving a pair of twins, one of which was a macerated, stillborn infant, while the other survived with severe brain damage which eventually caused death. In the present study, which include a high proportion of severely affected babies, neurological sequelae were not uncommon among the untreated or inadequately treated patients (Table I). In Negroes, according to the experience of Wiener and Wexler,⁶³ severe erythroblastosis resulting from ABO hemolytic disease appears to be more common than Rh hemolytic disease. Therefore, it is important for the clinician not only to be on the alert for instances of ABO hemolytic disease, but to recognize the severe form which will generally require treatment by exchange transfusion.

It has been demonstrated that Rh sensitization of expectant mothers can give rise to stillbirths, the stillbirth rate being correlated with the height of the maternal Rh antibody titer.^{58, 59} In the present series of 51 families, among 145 pregnancies there were as many as 7 stillbirths, indicating that ABO sensitization also can give rise to stillbirths. In the same 51 families there were only 15 spontaneous abortions, which is approximately the normal rate. When patients who were subject to repeated abortions were studied, however, it was found that such families show a significantly higher proportion of heterospecific marriages, that is, the husband is in an incompatible blood group more frequently than in control randomly selected matings.^{25, 60} This suggests that a certain proportion of cases of repeated abortions are caused by ABO incompatibility. Perhaps Family 30 in Table I represents such a case.

Summary

1. Observations on 51 families in which ABO hemolytic disease occurred are re-

viewed. In all but one of the families, the mothers were found to be Group O in conformity with previous reports. This is attributed to the ability of Group O mothers to form antibodies of specificity anti-C as well as anti-A and anti-B.

2. Affected babies were all either Group A or Group B. Of the Group A babies all but one appeared to be of subgroup A₁. The low incidence of subgroup A₂ babies is explained by the poor avidity of such red cells for isoagglutinins so that babies of this subgroup are less severely affected by maternal alpha isoantibodies.

3. Once severe ABO hemolytic disease occurs in a family, then, with rare exceptions, all future babies will be affected unless they belong to Group O.

4. The incidence of secretors and non-secretors among the Group O mothers in this series of families was the same as in the general population.

5. The incidence of nonsecretors among the affected babies, their siblings, and their fathers was lower than in the general population.

6. When the affected baby is Group A, the titer of the maternal serum for A cells tends to be higher than for B cells and, when the baby is Group B, the reverse is often true. This suggests that in many cases the baby's red cells or body fluids provide the antigenic stimulus accounting for the high titer of the maternal serums. In the remainder of the cases, the alpha and beta antibodies were of equal titers, suggesting predominance of antibody of specificity anti-C and presumably of heteroimmune origin.

7. It is pointed out that the attempt to distinguish between so-called natural and immune isoantibodies is based on a misconception. All alpha and beta antibodies appear to be of immune origin but, depending on the nature of the antigenic stimulus, the antibodies may be heteroimmune or isoimmune.

8. Two main patterns of ABO hemolytic disease appear to exist. In one, the maternal isoantibodies are chiefly of heteroimmune

origin (so-called "natural" antibodies) and the first-born incompatible baby is generally affected though the manifestations tend to be mild (icterus praecox). In the second form, one or more normal babies of an incompatible blood group may first be born; these babies are secretors and sensitize the mother so that subsequently born babies of incompatible blood group develop typical erythroblastosis. In many of these cases, however, in contrast to Rh hemolytic disease, the first-born incompatible secretor baby

may be severely affected.

9. In general, in cases of ABO hemolytic disease the titer of the maternal alpha and beta isoantibodies is markedly elevated. There appears to be a correlation between antibody titer and severity of the disease, though, as in Rh hemolytic disease, the correlation is not absolute.

10. The importance of recognizing ABO hemolytic disease is for the intelligent treatment of affected babies and for prognosticating the outcome of future pregnancies.

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ABO mother-infant incompatibilities

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THE diagnosis of hemolytic disease of the newborn, first elucidated by Levine and associates,^{32, 33} depended until recently on the ability to demonstrate an incompatibility between the blood of the mother and that of the infant. The incompatibility arises when the infant possesses an antigen which the mother does not possess and against which a corresponding maternal antibody can react. A progressive stride was taken when Coombs, Mourant, and Race⁵ first described the antiglobulin test. This test became important not only in the diagnosis of hemolytic disease of the newborn but also as a diagnostic tool in the field of immunohematology.

Some authors have attempted to test the specificity of eluates prepared from cord erythrocytes that exhibited a direct antiglobulin test.^{13, 14, 47} In some instances a strongly positive eluate could be obtained when the direct antiglobulin test was weak or negative.¹⁴ However, in cases of ABO iso-sensitization and when the classical technique was used, the antiglobulin test was found consistently negative by numerous authors.^{6, 14, 23, 26, 38, 42}

With the exception of ABO hemolytic

disease, there is little doubt about the value of the Coombs test in the diagnosis of hemolytic disease of the newborn.

In 1953, Rosenfield reported that, by using a modification of the direct antiglobulin test, he could obtain a positive result in all cases of ABO sensitization.^{43, 44, 46} Here then was a diagnostic tool of specific value. Before the availability of this test, the diagnosis of ABO hemolytic disease was based on indirect proof and as a result was incorrectly found to be of rare occurrence. With the application of this modified test, up to 5 per cent of all infants could be found A or B incompatible with a Group O mother and would exhibit sensitization via the specific A or B isoantibody (and occasionally a cross-reacting antibody). It should be emphasized that the majority of these infants were clinically normal, despite the fact that their erythrocytes were sensitized. Nevertheless, when studied as a group, they showed statistically significant deviations from the normal values for hemoglobin, reticulocyte counts, and serum bilirubin levels.^{22, 43}

We repeated this early work of Rosenfield in our laboratory and found an even greater incidence of positive antiglobulin reactions on cord bloods.^{21, 22} We were quite surprised when other laboratories could not confirm this work. The only workers who succeeded in confirming this study were Dunn⁸ in Vancouver and Chown⁴ in Winnipeg. It was this very discordance among workers concerning the value of the direct antiglobulin test in ABO hemolytic disease that prompted us to investigate further.

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Material and methods

When dealing with the antiglobulin reaction, it is important to keep in mind that this represents a very unusual type of agglutination reaction, and before reporting our results we wish to elaborate on this important concept. It was pointed out some time ago by one of us^{19, 20} that the usual agglutination reaction can be studied only by the "constant antigen" technique. The average erythrocytes or bacterial cells used in quantitative agglutination tests have a fixed statistical "load" of antigen which cannot be made to vary to a large degree. On the other hand, in the antiglobulin test, the first stage includes sensitization of the erythrocytes with an amount of antibody which can be varied in large proportions. Thus, the second stage of the reaction, wherein the sensitized erythrocytes are agglutinated by the antiglobulin serum, can be studied by the "constant antibody" technique by use of a fixed dilution of the antiglobulin serum against a gradient of decreasingly sensitized erythrocytes.²⁰ This technique demonstrates the prozone phenomenon^{19, 34} both in the antibody-excess and in the antigen-excess zones. It is in these "zones" that the sensitized cells will fail to be agglutinated and false-negative results will be obtained. This reaction pattern is often found with precipitating or flocculating antigen-antibody systems (e.g., the egg albumin/antioalbumin system or the diphtheria toxoid/antitoxin system).

This observation prompted us to use serial dilutions of the antiglobulin reagent routinely when the antiglobulin test was employed. The reagent was always prepared by us and it always possessed a very high titer. This technique allowed us to select the optimal antiglobulin dilution when cord erythrocytes were screened for ABO sensitization.

In order to obtain sustaining evidence that it was the specific anti-A or anti-B (which was transmitted by the Group O mother to the A or B infant) that was implicated, we performed the following tedious task: eluates from cord erythrocytes

were tested in parallel with the modified direct antiglobulin method on a large series of mother-infant couples.

Technique.

1. *Direct antiglobulin test.* First, 0.05 ml. of a suspension of cord erythrocytes was washed 4 times with isotonic saline. Following this, 0.05 ml. of the optimal dilution of the antiglobulin rabbit serum was added. This mixture was then centrifuged immediately at 500 r.p.m. for one minute. The suspension was promptly placed on a slide and read under low magnification.

2. *Elution test.* One milliliter of packed cord red cells, which had been washed 4 times with isotonic saline, was hemolyzed in 10 ml. of twice-distilled water for a period of 30 minutes. Then 1.1 ml. of 9 per cent saline was added and the stroma precipitated by centrifugation at 18,000 g. and at 10° C. The stroma was washed 4 times with isotonic saline.

The packed stroma was then suspended in 20 per cent bovine albumin and heated at 56° C. for 10 minutes. The suspension was immediately centrifuged at 18,000 g. for 3 minutes. The supernatant was tested by the indirect antiglobulin test with A₁, A₂, B, and O red cells.

Results

It should be emphasized that a 100 per cent correlation was found between the two tests. Specific antibody was eluted in all instances of a positive direct antiglobulin test and no antibody was found in the eluate when the direct antiglobulin test was negative.

In order to increase the accuracy of our estimations, ABO gene frequencies were calculated from the phenotype frequencies of the mother. Then the theoretical frequencies for mother and infant combinations were calculated and the results corresponded nicely with the observed frequencies for a sample of this size (Table I).

Among the 549 cases shown in Table I, there were 39 (or 7.1 per cent) which could be serologically classified as "latent hemo-

Table I. Frequency of latent hemolytic disease (positive antiglobulin test and elution test)*

Blood group of the mothers	No. of mothers (observed)	Mother and infant combinations		No. of mother and infant combinations		No. of mothers (calculated)
		Mother	Infant	Observed	Calculated	
O	273	O	O	171	192.31	272.85
		O	A	79	61.38	
		O	B	23	19.16	
A	202	A	A	130	126.32	201.80
		A	O	62	61.32	
		A	B	5	6.09	
		A	AB	5	8.07	
B	57	B	B	26	25.03	59.98
		B	O	19	19.16	
		B	A	5	6.09	
		B	AB	7	6.70	
AB	17	AB	A	8	8.08	17.36
		AB	B	7	6.70	
		AB	AB	2	2.58	

Gene frequencies: $p = 0.2249$
 $q = 0.0702$
 $r = 0.7049$

Genotypes: $OO = 0.4969$
 $AA = 0.0506$
 $AO = 0.3170$
 $BB = 0.0049$
 $BO = 0.0990$
 $AB = 0.0316$

*Latent hemolytic disease: O and A: 35 = 6.38 per cent; O and B: 4 = 0.73 per cent; total: 7.11 per cent. Classical Rh hemolytic disease: 4 cases = 0.73 per cent.

lytic disease" due to ABO incompatibility. We advocate the term "latent hemolytic disease" because, although there are no overt clinical manifestations in these cases, there are certain serologic findings which are constantly present. Such infants will show a positive modified direct antiglobulin test, increased red cell destruction, as shown by a fall in hematocrit, and a elevated reticulocyte count indicating an increased erythrocyte turnover.^{38, 39} Bilirubin values in individual cases are of no significant diagnostic value although there is a statistical difference in infants born of heterospecific as compared to homospecific pregnancies. This will be discussed later.

Of all the cases shown in Table I, the antiglobulin and elution tests were positive only when the mother was Group O and the infant either A or B. This association is statistically significant and in agreement with previous reports.^{29, 44, 46, 48} With few exceptions, of all the Group A infants show-

ing the positive tests, the cord erythrocytes were found to be of subgroup A₁. The infant's blood was ascribed the subgroup A₁ if there was a negative reaction with anti-H. If there was a positive reaction with anti-H it was classified subgroup A₂ (Table II).

The antibody specificities of the eluates, in those infants where both the modified

Table II. Mother-infant combinations in heterospecific pregnancies: normal cases and latent hemolytic disease

Mother and infant combinations	Latent hemolytic disease	Normal heterospecific pregnancy	Total
O and A ₁	26	14	40
O and A ₁ *	4	3	7
O and A ₂	4	22	26
O and A†	1	5	6
Total O and A	35	44	79
O and B	4	19	23

*Weak reaction with anti-A₁ sera, negative reaction with anti-H reagents.

†Subgroup not determined.

Table III. Specificity of the antibody eluted from the infant's erythrocytes

	<i>Infants of Group A</i>	<i>Infants of Group B</i>
Anti-A ₁	20	-
Anti-A ₁ + A	10	-
Anti-A ₁ + A + B	1	-
Anti-A ₁ + B	3	1
Anti-B	-	3
	34*	4

*In one case the eluate was not performed owing to a technical error.

antiglobulin and the elution tests were positive, have been tabulated in Table III. A₁, A₂, and B red cells were used in testing the antibody specificity. Cross-reactivity for the A and B antigens was found in only 4 cases.

Among the entire 549 cases in this study, there were 4 unselected cases of Rh hemolytic disease. This represents an incidence of 0.73 per cent as compared to 7.11 per cent for "latent hemolytic disease" (Table I).

The next step in this study was to follow carefully the infants during the postnatal period and thus evaluate the clinical import of the positive modified Coombs test. This will be reported elsewhere by one of us.¹¹ Suffice it to say at this time that these serologic findings were not observed in those infants born of heterospecific pregnancies where the modified antiglobulin test was negative. On the other hand, both the antiglobulin and the elution tests were consistently positive in all selected cases (not included in this series) of clinically evident hemolytic disease.

Comment

Review of the available literature attests the fact that ABO heterospecific pregnancy is by no means harmless to the progeny. One of the earliest reports was the demonstration by Hirsfeld and Zborowsky¹⁶ of a deficit in the offspring of heterospecific marriages. Also among the early reporters in this field were Kelsall²⁸ in Australia, Polayes⁴¹ in the United States, and Aubert and associates¹ in Great Britain. They all described cases of hemolytic disease, similar

to Rh cases, where the only detectable incompatibility was in the ABO system. Also the mothers' sera in these cases contained an unusual specific antibody, the in vitro properties of which will be discussed later.

Following the study by Hirsfeld and Zborowsky and in historical sequence was the description by Halbrecht¹⁵ of a mild and self-limited form of neonatal jaundice appearing early after birth (thus called "icterus praecox") and associated with a mother-infant incompatibility in the ABO blood groups. Later, more elaborate observations were made on this type of hemolytic disease by Hsia and Gellis¹⁷ and by Zuelzer and Kaplan.⁵² Grumbach and Gasser¹² described a form of hemolytic disease due to ABO antagonism in which the predominant clinical finding was a progressive anemia. This was confirmed later by Zuelzer and Kaplan.⁵²

Our own attention was directed to ABO maternal-fetal incompatibility in 1946. We described a familial syndrome with liver degeneration and kernicterus which we attributed to a cytotoxic action of the anti-A antibody.²⁶ This has been seen in 2 additional families since the original description. At the postmortem examination, one may see abnormal quantities of free iron in the spleen and in the liver. In some of the fatal cases, the large areas of fatty degeneration and/or necrosis seen primarily in the liver are consistent with a possible cytotoxic action of the offending antibody.^{26, 40}

Although there are few direct proofs, much incriminating evidence can be adduced in supporting the charges brought against an ABO heterospecific relationship. Many have already been mentioned and some bear repeating. Spherocytosis¹² and an increased red cell fragility⁶ are often found. There is frequently an elevated reticulocyte count indicating an increased turnover of erythrocytes. This can be shown by measurements in the survival rate of the infant's own red cells or by utilization of adult erythrocytes of the same group specificity which have been tagged with Cr⁵¹.^{6, 52} Cord bilirubin values are of little use in the indi-

vidual cases but statistical data show that the mean plasma bilirubin values are increased in those infants born of heterospecific as compared to homospecific pregnancies.²⁷ Statistically significant differences in cord bilirubin levels have also been demonstrated between those infants having a positive direct antiglobulin test and those with a negative test.^{22, 43, 44, 46}

The heterospecific relationship is a perplexing problem which has been difficult to solve. The accumulating evidence is still contradictory in many areas. As demonstrated by the fundamental work of Levine and collaborators,³³ the Rh situation is unique in that the disease never occurs unless the mother has been immunized by a previous pregnancy or transfusions. However, once the antibody is present, hemolytic disease involving the Rh-positive infant inevitably follows. In ABO heterospecific pregnancy, the antibody is regularly present in the mother's blood but it does not seem to affect the infant, at least not in a serious manner or with any significant frequency.

Studies on maternal blood. It would appear that studies concerned with the maternal antibody would pierce the hub of this serologic wheel. However, the wheel spins on and the hub remains hazy. Since the anti-A and anti-B are "naturally" present in accordance with Landsteiner's law, they are thought to be different from the Rh antibody, which is not normally present and perforce has to be of immune origin. Thus, many authors have attempted to invoke the existence of an "immune" antibody in those cases of ABO hemolytic disease. They believe the "immune" antibody to be a distinct entity, different at least from the so-called "natural" antibody or "regular agglutinin." Many characteristics of the "immune" group of specific antibodies have been described.

Wiener⁴⁹ and, independently, one of us in collaboration with Millet^{18, 20, 25, 36, 37} have shown that, following isoimmunization with the A or B antigen, the saline agglutinin is more active at body temperature. Thus the saline isoagglutinins share this property with

the anti-Rh agglutinins.^{30, 31} Boorman and co-workers³ recognized that the anti-A and anti-B following immunization, in contrast to the "natural" agglutinins, showed an increment in titer when human AB serum (diluted to 3 volumes with saline) was added to the test. This property has been observed by several authors, using different macromolecular media. The "immune" antibody appears to resist moderate heating^{2, 35} or neutralization by soluble blood group substances.⁵⁰ Partially neutralized sera, when heated, exhibit in vitro properties similar to anti-Rh sera; they produce a blocking effect in saline,² an elevated titer in protein or colloid media, and they sensitize the specific erythrocytes for the antiglobulin test.^{2, 35} The in vitro hemolysis of specific erythrocytes⁶ and complement fixing properties^{10, 50} have been ascribed to the "immune" type of the A and B antibody. The ability to opsonize has also been attributed to this "immune" antibody, as demonstrated by in vitro erythrophagocytosis tests.

Studies on infant blood. The direct proof that an immunologic mechanism is operating in hemolytic disease is afforded by the agglutination of the infant's red cells by an anti-human-globulin serum.⁵ It has been generally accepted that a positive direct Coombs test underscores the diagnosis of hemolytic diseases due to Rh maternal isoimmunization. Many workers were discontent when the direct antiglobulin test was discovered to be negative in ABO cases although there was a definite hemolytic disease present. Richardson-Jones¹⁰ described a two-stage antiglobulin reaction which involved first a rabbit anti-human-globulin serum and then a hen, anti-rabbit-globulin serum. This latter serum was supposed to show the fixation of the rabbit anti-human-globulin on the A or B cord erythrocytes that had been sensitized by anti-A or anti-B. Possibly because this technique is not practical for routine work there has been no large scale experience with it.

Rosenfield has shown that ABO sensitization can be detected on cord erythrocytes by a single stage antiglobulin test.^{43, 44, 46}

This may be done by use of selected anti-human-globulin sera, with immediate centrifugation at 500 r.p.m. The results are read under low magnification. This work by Rosenfield has been confirmed in our laboratory,^{21, 22} and the specificity of the antibody was controlled by elution tests. An additional test was conceived in our laboratory from the observation that the direct antiglobulin test, by the usual methods, may become strongly positive when adult cells are introduced into the infant's circulation.^{23, 42} In this particular method, a positive Coombs test could be obtained by mixing washed cord erythrocytes with adult erythrocytes of the same blood group, incubating at 37° C. for 30 minutes, and then submitting the mixture to an antiglobulin test. Because of the difficulties encountered in the usual direct antiglobulin test, some authors have found it necessary to implicate an excess of specific antibody in the cord serum as evidence of ABO hemolytic disease.^{7, 51} This has not been our experience or the experience of Rosenfield.⁴⁶

The expected frequencies of ABO and Rh incompatibilities in the Caucasian population are 20 and 12 per cent, respectively. These and other tabulations comparing the ABO and Rh systems appear in Table IV. If we define hemolytic disease of the newborn as manifesting 4 classical forms, that is, anemia gravis, icterus gravis, hydrops, and death in utero (as seen with the Rh

Table IV. Comparison between ABO and Rh

	ABO (%)*	Rh (%)*
Potential antagonism (Caucasian populations)	20	12
Hemolytic disease of the newborn (classical)	0.025-0.055	0.25-0.50
Icterus praecox	0.70-2.70	?
Latent hemolytic disease	Around 7.0	Around 0.05
Kernicterus in untreated cases	0.1-0.4	0.2

*These frequencies represent estimates per one hundred unselected pregnancies.

Table V. Ward exchange, the Mount Sinai Hospital (1955-1957)*

Serologic incompatibility	No.	Frequency
ABO	13	0.268 (1/373)
Rh	10	0.206 (1/486)
Both	23	0.474 (1/211)

*Total ward infants delivered: 4,854.

system), then the incidence of this disease due to ABO is 10 times less frequent than that due to an Rh incompatibility. The incidence of classical ABO hemolytic disease among all births has been placed by Haberman and co-workers¹⁴ at 0.024 per cent, by Elbel and Prokop⁹ at 0.025 per cent, and by Hubinont and associates²⁴ at 0.055 per cent.

Icterus praecox, as defined earlier, is very rarely seen in Rh incompatibility, whereas in ABO incompatibility the incidence lies between 0.70 per cent¹⁵ and 2.7 per cent.¹⁷ Latent hemolytic disease, in accordance with the definition given earlier, is far more frequent in the incompatible ABO group than in the Rh group. The syndrome is seen in only one tenth of the Rh incompatible cases.

The fate of the afflicted infants hinges on the important sequel of kernicterus. Before the era of exchange transfusion, approximately 50 per cent of the Rh cases terminate in death or serious neurological sequelae. The incidence of kernicterus in the untreated infants would then be around 0.2 per cent to 0.25 per cent. From the available statistics and mainly from the studies of Zuelzer and Kaplan,⁵² the incidence of kernicterus in untreated cases of icterus praecox has been estimated to be about 15 per cent. The over-all incidence would then lie between 0.1 per cent and 0.4 per cent, which is the same order of magnitude as seen in the Rh cases. Confirming evidence along these lines can be found in Table V, which shows the statistics in exchange transfusion at the Mount Sinai Hospital of New York from 1955 through 1957. It should be noted that there were more exchange transfusions performed for ABO than for Rh hemolytic

disease. All cord bloods were routinely tested with the modified antiglobulin test.⁴⁵

At the present time, an ABO incompatibility is more dangerous than an Rh incompatibility because it tends to be overlooked by all concerned, i.e., the practitioner, the obstetrician, the pediatrician, and even the clinical pathologist or hematologist. In our opinion, prenatal testing for ABO immunization is impracticable. The only way to make an early diagnosis is to study the infant at the time of birth. The disease tends to strike those incompatible infants born of Group O mothers. The modified direct antiglobulin test, properly used by any blood grouping laboratory, can be of diagnostic and prognostic value. This test can be used as a weathervane for impending hemolytic disease. Once the diagnosis of ABO latent hemolytic disease has been made, daily hematologic studies (including bilirubin determinations) can be carried out on the infant. The onset and progression of jaundice is evaluated far better in the test tube than it is by the human eye. Indifference and negligence in this small sphere can spell the difference between health and permanent disability.

Summary

1. An incompatible ABO mother-infant relationship is not without risk to the infant. The ABO system is just as important as the Rh system as a cause of permanent disability. Perhaps at the present time it is more important, because an ABO incompatibility tends to be overlooked.

2. The concept of latent hemolytic disease has been stressed and is based on serologic findings. The significance of performing the modified antiglobulin test on all ABO incompatible infants born of Group O mothers has been discussed.

3. A positive modified antiglobulin test has been confirmed by a positive elution test in every case studied. The test has both diagnostic and prognostic value and, when positive, it may well herald the onset of jaundice.

4. We advocate that all cord bloods (primarily in those suspected of an ABO incompatibility) be tested routinely by the modified antiglobulin method—for this simple procedure might well spell the difference between health and disability later in life.

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Hemolytic disease of the newborn due to anti-c

A case report

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IN THE field of immunology the c antigen has generally been regarded as a weak immunizing agent. However, it appears that when administered intravenously as a result of blood transfusion in association with pregnancy, the immunization process which is developed could be as severe as any occurring in cases of hemolytic disease of the newborn. In previous papers^{1, 2} one of us (MDA) presented a method of detecting the presence of Rh sensitization in pregnant patients. All expectant mothers receive a routine blood examination, and the serum of those found to be Rh negative is then further examined for the presence of the Rh antibodies. This method fails to demonstrate the isoimmunization process affecting the Rh-positive prenatal patient.

Considerable knowledge has been gained during recent years concerning the pathogenesis of hemolytic disease of the newborn. There is an increasing volume of well-documented evidence which indicates that Hr sensitization studies represent an important tool in the diagnosis of this disease.

The purpose of this report is to describe a case of hemolytic disease of the newborn due to anti-c where maternal sensitization re-

mained unsuspected because the patient was Rh positive.

Case report

A 28-year-old white woman, para 2-1-0-1-1, whose expected date of confinement was July 23, 1955, was first seen on Jan. 5, 1955. Her prenatal course was uneventful. She had been married twice. During her first marriage she had experienced a full-term pregnancy in 1946 and a miscarriage in 1948, at which time she required a transfusion of three pints of blood.

The patient subsequently remarried and, in July, 1955, was delivered of an erythroblastotic baby at term. The studies of the antigenic factors are shown in Table I.

Immediately after delivery, an exchange transfusion was considered mandatory. A considerable amount of time was required to find a compatible donor. Several donors, Type O, Rh negative (cde/cde), were tested and the results showed gross agglutination in the major side. One donor, Type O, Rh positive-hr' negative (CDe/CDe), showed no agglutination. This latter donor's cells lacked c antigen.

Antibody tests indicated that the mother was strongly sensitized to the c factor (hr'). The anti-c antibodies were clearly demonstrated by the albumin and by the indirect Coombs test with a titer of 64. To further substantiate the specificity of this antibody (anti-c), examinations were performed with a battery of test cells (known antigens) and with the aid of special antisera (Kell, Cellano, M, N, s). The results indicate the presence of a single type of anti-

From the U. S. Army Hospital, Sandia Base.

†Deceased.

Table I. Studies of antigenic factors involved

	ABO	C	D	E	c	e	Genotypes
H.F.H., second husband	O	-	-	-	+	+	cde/cde
P.A.H., wife	O	+	+	-	-	+	CDe/CDe
Child A, living and well	O	+	+	-	+	+	CDe/cde
1948, miscarriage	?	?	?	?	?	?	Undetermined
3 blood transfusions Type O, Rh positive	O	?	+	?	?	?	Undetermined
1955, propositus	O	+	+	-	+	+	CDe/cde

body mainly characterized by its reactivity to the c factor. These findings were confirmed by another observer.³

The serological studies with use of maternal serum and propositus cells showed a positive reaction as indicated by the albumin and by the indirect Coombs test with a titer of 64. This important finding represents a valuable contribution to the diagnosis of the case, since it demonstrates incompatibility between mother and offspring. Immediately after birth, laboratory findings showed: hemoglobin 10.9 Gm. per 100 c.c.; erythrocytes 2 million per cubic millimeter; differential count: neutrophils 90 per cent, eosinophils 2, lymphocytes 8 per cent, basophils 0, monocytes 0; total bilirubin 21.6 mg. per 100 c.c.; Rh factor, positive (tube test); blood morphology: marked hypochromia, anisocytosis, poikilocytosis, and polychromatophilia, moderate number of macrocytes and spherocytes, and about 2,000 nucleated erythrocytes per 100 leukocytes. The nucleated erythrocytes were classified as follows: 0.5 per cent proerythroblasts; 4.5 per cent erythroblasts, and 95 per cent normoblasts. Direct Coombs test, negative. This procedure was performed in duplicate.

An exchange transfusion of 500 c.c. of compatible blood was carried out via the umbilical vein. Seventy-two hours post transfusion the baby appeared somewhat improved. During the first 5 posttransfusion days, jaundice and splenomegaly remained. Three weeks after birth the baby became symptom-free and was discharged from the hospital.

Comment

Two aspects of the subject warrant further consideration: (1) the causative agent of this sensitization process; (2) the presence of a negative Coombs test.

Table I shows the antigenic factors involved. The maternal genotype (CDe/CDe) strongly suggests a homozygosity at the locus

C. This would indicate the presence of a double amount of C antigen and the absence of a c antigen. In our experience we have never seen anti-c circulating in a gravida 3 patient unless a history of blood transfusion was obtained. Immunization caused by the c antigen will depend largely upon the quantity of antigen administered and the patient's ability to develop antibodies. In the case under consideration it appears that the primary stimulus for the antibody formation was the period of gestation of Child A. This stimulus was subsequently followed by the blood transfusions received at the time of miscarriage in 1948. As indicated in Table I, the presence of the c factor in the transfused blood was not determined; nevertheless, it could have been present as has been suggested.⁴ This may have been possible since the probability of a negative person's receiving c-positive blood is about 10 per cent. It is probable that further stimulation occurred during the present pregnancy. Cases similar to this have been reported,^{5, 6} and these reports have demonstrated an association of this type of sensitization process with transfusion following pregnancy. The presence of anti-c in the serum of a patient will lead to confusion unless its mode of action is kept clearly in mind. On one occasion a baby with hemolytic disease of the newborn was given exchange transfusion of Rh-negative blood and as a result of the anti-c mechanism the disease affecting the baby became more severe.⁷

It is not surprising to find that in some instances of hemolytic disease of the newborn a negative reactivity in the Coombs test has been observed. A careful review of these cases indicates the presence of a sensitization

process due to differences in the types of blood between mother and child. These differences fall within three categories: the ABO system, the Rh system, and the Hr system. In the case here discussed it is reasonable to believe that the lack of reactivity in the test represents an atypical behavior of the factors involved. The fact that one of these factors (anti-c) is a result of a sensitization process caused by a combined antigenic stimulation (transfuso-pregnancy) may have some bearing. In addition, it is noticed that this same factor (anti-c) acts better when suspended in a protein media. This characteristic leads us to suggest the

presence of inhibitors or the possibility of prozone phenomenon, producing substances which can interfere in the test, resulting in a false-negative reaction.

Summary and conclusion

A case of hemolytic disease of the newborn due to anti-c successfully managed by transfusion, is reported.

An antibody identified as anti-c remained unrecognized during the prenatal period of a Rh-positive patient.

The difficulty in finding compatible donors is emphasized.

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CURRENT OPINION

Clinical problems

Anorexia nervosa

Case presentation

Patient L. A., 18 years of age, unmarried, complained of loss of weight, amenorrhea, dryness of the skin, ease of fatigue, generalized weakness, periodic bilateral lower abdominal discomfort, and bloating. During the preceding 18 months the patient's weight had gone from 112 to 83 pounds, a 28 pound loss. Ten of these pounds had been lost in the past 10 weeks.

The first menstrual bleeding occurred at age 13 years and consisted of spotting for one day only and was not accompanied by pain. At the age of 15 years uterine bleeding occurred for the second time. This consisted of spotting for one day and was accompanied by discomfort and bloating similar in character to that which now occurs in periodic episodes while the patient is amenorrheic.

The bilateral lower abdominal discomfort and bloating have occurred periodically on the thirteenth and fourteenth of each month for a duration of 2 days each month for the past 5 months. There is no periodic breast tenderness.

Past history. The development of physical stature during childhood was apparently normal except that the patient was large for her age when she was in the second and third grades of school.

Axillary and pubic hair and the breasts developed between the ages of 8 and 9 years. Since then there has been but little increase.

At the age of 13 years the patient's basal metabolic rate was -32. Thyroid extract, 180 mg. daily, was administered until she

was 14. The drug was stopped for an indefinite period and then resumed at the level of 90 mg. daily and, at age 18 years, was increased to 120 mg., which was being administered at the time of admission. Upon this dosage the basal metabolic rate was -22 per cent, cholesterol 184 mg. per cent, and the protein-bound iodine 3.9 μ g per 100 ml. These values were obtained 8 weeks prior to hospital admission. The dryness of the skin, ease of fatigue, and generalized weakness had not improved with this therapy.

Physical examination. With the exception of undernutrition, dryness of the skin, hypotension of 84 systolic, 60 diastolic, and a pulse rate of 55 to 60 per minute, the physical findings were within the range of normal.

Laboratory tests and results.

Blood. Hemoglobin 13.2 Gm.; red blood count 4.35; white blood count 5,300; erythrocyte sedimentation rate 4 mm. per hour; hematocrit determination 45 per cent.

Urine. Specific gravity 1.010; albumin 0; sugar 0; microscopic negative.

Chemistry. BUN 9.7 mg. per cent; calcium 10.2 mg. per cent; phosphorus 4.75 mg. per cent; cholesterol 230 mg. per cent; sodium 146 mEq.; potassium 3.5 mEq.; chlorides 105 mEq.

Glucose tolerance. Fasting, 65 mg. per cent; 1/2 hour, 47; 1 hour, 46; 2 hours, 51; 3 hours, 52.5; 4 hours, 67. 17-Ketosteroids, 10.4 and 14.5 (normal 6 to 7) mg.; 11 oxysteroids, 2.7 and 4.8 (normal 4 to 8) mg.

Roentgenogram findings. Roentgenograms

of the skull and chest showed no abnormal findings.

Problem: Would you discuss the possibilities of diagnosis, the addition of other studies that might aid in the establishment of a diagnosis, and the management of this patient?

Consultation

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This patient presents a fairly classical picture of a syndrome which easily can be confused with several other disease entities. Several pertinent points in the history and work-up make the diagnosis fairly simple, but the management may prove far more difficult. The protean manifestations and the generalized nature of the complaints as well as the involvement of several different organ systems make one think immediately of an endocrine disturbance. The signs and symptoms as outlined may be due to disorders of the pituitary, thyroid, adrenal, ovaries, or hypothalamus. Constitutional diseases, of course, must be considered.

The slow pulse, dry skin, fatigability, hypoglycemia, and markedly lowered basal metabolic rate permit a diagnosis of hypothyroidism to be entertained. However, hypothyroidism does not give such a marked weight loss and evidence of cachexia as seen here. The normal cholesterol value and the nearly normal protein-bound iodine level would militate against such a diagnosis. Confirmation that this is not a thyroid disorder is furnished by the lack of response to thyroid medication. In severe hypothyroidism, a dosage as large as that given this patient would probably provoke decided untoward reactions unless it was given in very small doses and very gradually increased to the 180 mg. level. Likewise, failure of response to the medication nearly completely rules out thyroid deficiency. It is conceivable that this patient could not utilize the particular

form of thyroid given her, but this is problematical.

Pituitary disease is a very tempting diagnosis. Certainly the patient presents evidence of multiple glandular deficiencies along with evidence of some element of precocity which may be related to abnormal pituitary function. It is felt more likely, however, that her development of secondary sex characteristics at a somewhat earlier period than usual probably does not represent any disease but simply a premature, but normal, puberty. The elements of precocity, such as pubic and axillary hair growth, breast development, and increase in physical stature between the ages of 8 and 9 need not be construed as a real pituitary disorder, but merely as evidence of premature release of pituitary gonadotropins at a somewhat earlier than expected time. The clinical picture is a beautiful description of pituitary cachexia (Simmonds' disease) except for the presence of pubic and axillary hair (which nearly always disappear in hypopituitarism) and the occurrence of cyclic episodes of pelvic congestion and bloating suggestive of that seen during the menstrual cycle. The laboratory findings of normal hemoglobin and hematocrit levels as well as fairly normal serum electrolyte values are strong evidence against such a diagnosis, and normal 11-oxycorticosteroids and elevated 17-ketosteroids fairly well exclude such a diagnosis.

The precocious breast development and growth of pubic and axillary hair, usually referred to as the adrenarche, as well as the elevated urinary 17-ketosteroids, might suggest some form of increased adrenal function. The clinical picture, however, is not compatible with continued and increasing hyperadrenalism (adrenogenitalism). Certainly, the appearance of the patient is more like that seen in decreased adrenal function (Addison's disease). Again, however, the absence of anemia, pigmentation, or loss of pubic or axillary hair, the normal serum electrolytes, and the normal to high urinary steroid values seem to negate such a possibility.

The amenorrhea leads to speculation that

this patient may have a primary ovarian disorder. However, the good breast development and nearly normal pubic and axillary hair bespeak of good pituitary-ovarian-adrenal balance. The functional ovarian tumors which could be malignant and lead to general cachexia when widespread are unlikely in that other manifestations would appear from the excessive and unbridled hormonal activity.

Organic hypoglycemia may be considered because of the glucose tolerance curve, but this is not in harmony with the remainder of the clinical picture. Liver disease, widespread carcinomatosis, tuberculosis, chronic disease processes, and other general debilitating diseases are worthy of mention, but there is no evidence of any of them.

It seems much more likely that the picture presented is due to a hypothalamic disorder, either functional or organic. An organic lesion in the region of the hypothalamus should always be thought of in patients with precocious puberty, and a progressive tumor or vascular disease could account for the symptomatology. Certainly, such a lesion must be ruled out. In spite of this, however, this patient presents the textbook picture of the functional hypothalamic disturbance, anorexia nervosa. This disease entity can account for the loss of weight, amenorrhea, dryness of the skin, fatigability, weakness, hypotension, bradycardia, hypoglycemia, low basal metabolic rate, and the increased 17-ketosteroid excretion.

An excellent differential point in the diagnosis of anorexia nervosa is that loss of pubic and axillary hair seldom occurs in this disorder; if any change in hair growth is noted, it is usually in the form of an increase of the fine, downy hair over the entire body. The cyclic occurrence of lower abdominal bloating and discomfort as evidence of some remnant of cyclic ovarian function is somewhat disconcerting, but this may merely indicate that pituitary-ovarian function has not been totally arrested, or the occurrence may be a rhythmic hypothalamic phenomenon not based on any organic dysfunction. Moreover, such cyclic discomfort could also

suggest some type of block preventing the expulsion of menstrual blood, but the occurrence of two menstrual periods at an earlier time in her life and no evidence of a pelvic tumor seem to vitiate this possibility.

Further work-up should include a complete neurological survey to rule out an organic lesion in the region of the hypothalamus as a matter of prime concern. A better idea of exact pituitary and ovarian function could be ascertained with vaginal smears, endometrial biopsy examination if possible, and urinary gonadotropin assays. It hardly seems necessary to undertake an extensive radiologic work-up for tuberculosis or some hidden malignancy, but this might be considered in passing. A psychiatric evaluation is imperative in these patients.

In managing the patient with anorexia nervosa it is of paramount importance to discern, if possible, the exact factors contributing to the continuation of the disease. Thus, exploration of the total personality make-up is necessary. It is conceivable that the precocity placed this child apart from other children and a deep-seated neurosis may have resulted from it. A complete change in environment (school, domestic, and social) is often of some value and should be undertaken as soon as the diagnosis is made. Forced feedings, both oral and parenteral, are necessary. Cyclic estrogen and progesterone to induce monthly menses has a place in treatment primarily for its salutary psychogenic effect. Norethindrone (Norlutin) may be used for this purpose to great advantage. In a dosage of 5 mg. four times daily for 20 days in each month, a withdrawal period will usually occur, although one or 2 months may be needed before results are obtained. Norethindrone is of especial value because it is a potent progestational agent with inherent estrogenic and androgenic properties and, thus, will induce withdrawal bleeding. It is also a good anabolic agent and stimulates the appetite. The management of the patient with anorexia nervosa is long and frequently difficult, but attention to every detail may prove rewarding.

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That there are disturbances of endocrine function in this patient would be implied by the recorded data: low basal metabolic rate determinations, the flat glucose tolerance curve, and the failure of normal menstruation. The basic question revolves around whether these phenomena represent primary disturbances of function of the thyroid gland and ovaries, whether these represent defects secondary to pituitary dysfunction, or whether these are alterations in function of otherwise normal structures due to environmental factors.

It would appear that growth and development transpired in normal fashion until adolescence. The first recorded abnormality was then observed, namely, depressed function of the thyroid gland. The frequency of occurrence of this phenomenon during puberty, post partum, and during the menopause is well known. Whether this transpires as a result of failure of end-organ function or as a result of other hormonal factors producing an inhibition of thyrotropic hormone is not known. Correction of this deficiency, however, altered neither the symptoms nor the findings and did not prevent the development of other manifestations. The recorded investigation was motivated primarily because of the development of a new symptom—progressive weight loss.

Of the additional data obtained from this investigation, the flat glucose tolerance curve requires explanation. Although compatible with adrenocortical hypofunction, the presence of normal electrolytes, normal urinary 17-ketosteroids, and low normal 11-oxysteroids represent strong contrary evidence. The occurrence of flat glucose tolerance tests in the presence of starvation or hypothyroidism is well known and suggests altered utilization rather than defective carbohydrate metabolism. That is, with defective glycogen as well as lipid reserves, the impact of the glucose load was insufficient to elevate the blood sugar as would normally occur.

In 1873 and 1874 Sir William Gull^{1, 2} reported on 3 patients observed at Guy's Hospital, London, in which a lack of appetite was associated with a "morbid mental state." Even antedating Gull's description of anorexia nervosa, there had been other reports—one by Richard Morton in 1694.³ He discussed "nervous consumption" regarding the immediate cause of this "distemper" to be in the "system of the nerves." Lasègue⁴ in 1873 likewise reported classical symptoms of this disease and emphasized the emotional factors present in his patients. Through the years many reports of additional cases have appeared as well as varying recommendations concerning treatment. One of the excellent review articles together with a report of data on 28 additional patients was published by Beck and Brøchner-Mortensen.⁵ Their data were most complete and merit comment. Glucose tolerance tests were performed on 10 of the 28 patients. Seven of these were flat curves. Twenty of the 28 patients had low (–11 to –37 per cent) basal metabolic rate determinations which rose coincident with clinical improvement. Six of the 7 patients with flat glucose tolerance curves had low basal metabolic rate determinations. Urinary gonadotropins were assayed in 16 patients and all were less than 30 to 50 mouse units or below the upper limit of normal. Urinary estrogens were determined in 17 patients and the values in 14 were low. This is in agreement with other observations reported by McCullagh,⁶ who used estrogen bioassay, and by Richardson,⁷ who employed vaginal smears as an index of estrogen production. While these data suggest that the amenorrhea is related to the low estrogen production, no explanation of how this occurs is offered.

The patient under discussion fulfills the classical descriptions of anorexia nervosa in all categories. While endocrinologic approaches to the problems may be employed, these would largely be in the category of symptomatic treatment only, to the neglect of the underlying psychiatric disturbances which result in the production of the problem.

It is of interest to speculate upon the mechanisms by means of which these profound endocrine disturbances arise. For the moment, there is no forthright explanation. In a genetic aberration of chickens, known as "frizzle fowls," born with no feathers, Landauer described all varieties of hormonal defects occurring which completely disappeared when the chickens were supplied with sweaters. Under these circumstances, the fowl became normal in all regards except for the continued absence of feathers. This clearly depicts the role of environment as related to endocrine function. Perhaps the occurrence of endocrine dysfunction in patients with anorexia nervosa may be explicable upon the same basis.

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Editor's comment

The two Consultants have covered the aspects of anorexia nervosa in a beautiful manner, brief but thorough, and have presented well the difficulty in establishing the diagnosis and in conducting the management. The importance of psychiatric evaluation is stressed and is important.

In the patient presented, a neurological survey was accomplished but no lesion was identified.

This patient has had a complete change of environment, cyclic estrogen and progesterone therapy, forced feedings, and psychiatric care without improvement up to the present time.

Intrapartum sepsis

Case presentation

Mrs. L. S. C., aged 33 years, gravida xi, para ix, had an obstetric history of 8 normal spontaneous deliveries of living infants, one spontaneous abortion at two months' gestation, and in the last pregnancy, in 1957, a double footling stillbirth. She had had normal blood pressures with the exception of a slight elevation during the last pregnancy. She stated she had always had a relatively low blood count, and a sickle cell trait was demonstrated. During the current pregnancy she had regularly attended a prenatal clinic; the urine had been normal, and the blood pressure had been consistently 130/90 with the exception of one rise to 150/90. On Dec. 10, 1958, the hemoglobin was 7.6 Gm. but responded to intramuscular injection of iron-dextran complex (Imferon) and on Mar. 24, 1959, the hemoglobin was 10.2 Gm. and hematocrit was 31 per cent.

The patient was first seen by the delivery service when she entered the hospital with mild irregular contraction on April 16, 1959, at 2:50 A.M. The expected date of delivery was April 5, 1959, and the membranes had been ruptured for 11 days on admission. A physician had been called to the home on April 7 (36 hours after rupture of the bag of waters). The temperature and pulse were normal at that time. The cervix was said to be long and closed. Hydrostreptomycin, 0.5 Gm., and 400,000 units of penicillin were given prophylactically and bed rest was advised. Two days before admission of the patient to the hospital the physician again visited the home and found that the patient's pulse and temperature were normal. The obstetric conditions were unchanged; fetal heart tones were present, and the amniotic fluid was clear. It was specifically stated that there was no evidence of infection. At that time, however, another 0.5 Gm. of hydro-

streptomycin and 400,000 units of penicillin were given prophylactically.

The findings on admission to the hospital were: temperature 99.8° F., blood pressure 136/86, pulse 96, and weight 283 pounds. Fetal heart tones were absent. The abdomen and fundus were soft and nontender. Fetal parts could be palpated only with difficulty because of the obesity. The cervix was long and closed; the presenting part was floating, and there were mild irregular contractions. X-ray examination of the abdomen revealed a large fetus in cephalic presentation. One million units of aqueous penicillin and 600,000 units of procaine penicillin were given intramuscularly within an hour of admission. The 600,000 units of procaine penicillin were to be repeated twice daily. An intrauterine sepsis was recognized but the patient was considered to be in early labor and no particular alarm was felt for her safety.

At 3:00 P.M. (12 hours after admission) the patient had a sudden severe chill and the temperature rose to 101.8°. Fifty cubic centimeters of a foul-smelling reddish brown vaginal discharge was noted for the first time. The uterus was tense and tender and the patient complained of epigastric distress. Blood taken at this time failed to clot. Two grams of fibrinogen was given. Whole blood was prepared but time did not permit its use. The blood pressure was 100/60 and the pulse 110. Tetracycline, 1 Gm. in 5 per cent dextrose in water, was started intravenously (about 300 c.c. of which was given). The cervix was 3 cm. dilated. Contractions were weak and no more vaginal bleeding occurred. The temperature rose to 102.4° F.

In rapid sequence the blood pressure dropped and became unobtainable in spite of nasal oxygen and intravenous Coramine, and

a bloody, frothy material came from the mouth and nose.

At 4:00 P.M. (approximately one hour after the chill and 13 hours after admission to the hospital) the patient died.

- Problem:** 1. Please comment on the diagnosis and management of this case.
2. Discuss the problem of sepsis in obstetric patients today.

Consultation

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The patient's prenatal care was wholly adequate until the time that her membranes ruptured spontaneously at home. In summary, she was a hugely obese, grande multipara of 33 years with very mild chronic hypertensive vascular disease, in whom a sickle cell trait had been demonstrated. Because of 8 living children, hers was an excessively valuable life from the community's standpoint.

She was seen at home by a physician 36 hours after the membranes ruptured. Under the magnificent illumination which hindsight bestows upon us all, it is apparent that from this point on a series of medical errors were made. The initial mistake was not to hospitalize the patient at once. Intrapartum infection cannot be prevented by antibiotics; one questions how much they even reduce its incidence. It is reasonably safe to allow the cooperative, educated, privileged private patient living in clean surroundings to remain at home after the membranes rupture, but it is dangerous to permit the underprivileged, less educated clinic patient residing in relatively unclean surroundings to do so. The small, single dose of antibiotics (400,000 units of penicillin and 0.5 Gm. of streptomycin)

cin) treated the doctor by falsely reducing his concern but did not treat the patient. If for some reason hospitalization could not be carried out, 500 mg. four times a day of a broad-spectrum antibiotic like chloramphenicol would be more likely to create a protective umbrella against intrapartum infection than the therapy ordered.

More than a week later the patient was revisited by the physician and in spite of the fact that the membranes had been ruptured for 9 days and the patient was past term, hospitalization was not ordered.

On admission to the hospital the patient's degree of sepsis was misjudged and mistreated. A relatively small dose of antibiotic was given and the wrong antibiotic chosen. In our experience, a fair proportion of intrapartum infections are due to the colon bacillus and other penicillin-resistant organisms. Certainly 1.2 million units of penicillin per day would only be effective against penicillin-sensitive organisms. The patient should have been given a broad-spectrum antibiotic in addition to the penicillin or perhaps a broad-spectrum antibiotic, such as chloramphenicol, alone.

No culture was taken of the cervical-uterine contents to establish the specific organism and to set up drug sensitivity studies. A Gram-stained smear conceivably might have shown the presence of gram-negative organisms and the uselessness of penicillin.

Despite the fact that a dead fetus was diagnosed, no studies were made on the ability of the blood to clot, much less the fibrinogen level. The terminal failure of the blood to clot may have been due to profound, rapidly developing sepsis and, if so, may not have been apparent on admission. On the other hand, the hypofibrinogenemia may have been secondary to the dead fetus and, if so, evidence of it would have been present on admission. It is difficult to understand why blood was not matched and put on reserve as soon as the patient was admitted. Certainly an obese grande multipara with a dead baby and intrapartum infection gives promise of obstetric difficulty.

When the cataclysmic end occurred, it

was probably too late to do anything. I have seen 2 patients die quite similarly in mid-pregnancy from an overwhelming intra-abortal sepsis with the colon bacillus. Both appeared mildly ill and, within several hours after admission, both developed a chill and went into profound collapse. Intravenous norepinephrine and hydrocortisone acetate were powerless to relieve the shock, and death occurred a few hours later.

Of course the death of the patient under discussion may have been due to amniotic fluid embolism secondary to the dead fetus. If so, 2 Gm. of fibrinogen was inadequate therapy; probably 6 or 8 Gm. was necessary. The unavailability of blood for transfusion is regrettable.

It is interesting to speculate what would have happened if the patient had been admitted to the hospital immediately after the membranes ruptured. Would a better regimen of daily antibiotics have prevented the fatal infection? Would the cleaner environment of the hospital make her less likely to become infected? Is it possible that enforced bed rest would have contributed to her safety? As far as I know, no one can categorically answer these three questions in the affirmative, yet I feel the patient would have been alive today if hospitalization, etc., had been instituted. She may have developed an intrapartum amnionitis and deciduitis, but I doubt that it would have been sufficiently severe to cause her death.

I know it may appear brash and iconoclastic to some readers, but I would have started the patient on a minute dose of intravenous Pitocin, using the variable speed infusion pump, 48 hours after rupture of the membranes, despite her great parity, the floating vertex, and the unfavorable cervix. If 6 or 8 hours of weak stimulation had not initiated labor, I would have desisted temporarily and very likely labor would have come on spontaneously within 12 hours. If not, I would have begun the Pitocin infusion again. If during attempts at induction evidence of intrapartum infection had appeared, labor had not begun, and the fetus were still alive, I hope, despite the patient's obesity,

I would have been bold enough to perform a cesarean section on behalf of both the fetus and the mother.

The gravity of an intrapartum infection is difficult to gauge by maternal temperature and pulse. Most certainly babies die of intrapartum infection when the mother's temperature elevation is minimal. Yet when born the infant has the telltale putrid odor, and on microscopic section the placenta has evidence of profound inflammation.

I fear intrapartum infection more than puerperal infection. The latter has become relatively rare and happily amenable to antibiotic therapy. On the other hand, intrapartum infection seems to have shown no radical reduction in incidence and it remains resistant to specific therapy. Perhaps we ought to use much higher dosages of antibiotics in the treatment of intrapartum infection than in the treatment of puerperal infection with the goal of producing high amniotic and fetal blood levels.

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In studying the data submitted, one's attention is focused on the fact that a patient at term was allowed to remain at home 11 days after rupture of the bag of waters. When a similar situation occurs in a markedly premature gestation the delay of labor in the hope of obtaining a larger baby is sometimes advocated. This is not without hazard but might conceivably serve a useful purpose.

In my experience, however, the hazard of infection to both mother and baby has frequently cancelled any presumed advantage. In the case under consideration, there is no valid reason for delay in stimulating labor.

The local doctor apparently was conscious of the possible danger from infection since he empirically administered 0.5 Gm. of hydrostreptomycin and 400,000 units of penicillin on April 7 and again on April 14. It is doubtful whether or not antibiotics are useful before the onset of labor, but if one does subscribe to their use more adequate dosage would seem appropriate.

This brings us to the hospital admission at which time the patient was in early labor. She had a temperature of 99.8° F., and pulse of 96, and fetal heart tones were absent. The abstract states "an intrauterine sepsis was recognized." We have to assume this was deducted from the temperature and pulse and death of the baby since the uterus was said to be nontender and foul amniotic fluid was not observed until later in the course. Penicillin was used but not in massive doses since there was no particular alarm felt for the patient's safety. In retrospect, larger doses of penicillin combined with a wide-spectrum antibiotic might have been helpful—although at this late stage it is by no means certain that anything would have altered the course.

Twelve hours after admission a chain of events developed that within an hour led to the patient's death. To reiterate: (1) chill, (2) temperature elevation to 101.8° and 102.4° F., (3) tense and tender uterus, (4) severe epigastric distress, (5) foul vaginal discharge, (6) failure of blood to clot but no evidence of frank hemorrhage, (7) precipitous drop in blood pressure, and (8) frothy bloody fluid from the nose and mouth.

It would appear that the patient died from pulmonary embolism; whether multiple septic emboli or amniotic fluid emboli would have to be determined by postmortem examination. The former seems more probable, the predisposing factors being sepsis from prolonged rupture of the bag of waters augmented by a longstanding anemia.

Amniotic fluid embolism is usually associated with a tumultuous labor and more recent rupture of the bag of waters. Oxytocics were fortunately not used else they would most assuredly have been suspect if

not blamed for the subsequent course.

Once the catastrophic episode occurred, in all probability, nothing could have altered the fatal outcome. Nasal oxygen, stimulants, and wide-spectrum antibiotics were used. Two grams of fibrinogen was given but up to 8 or 10 Gm. would probably have been required to restore normal clotting mechanism. It is well that the whole blood was not given since there was no frank hemorrhage and since there was evidence of pulmonary edema. Three hundred cubic centimeters of 5 per cent glucose containing tetracycline probably had no significant bearing on the outcome.

The best treatment here would have been prophylaxis of the sepsis by induction of labor following the spontaneous rupture of the bag of waters.

During the past decade we have grown far too indifferent to the hazard of sepsis. The antibiotics and availability of blood have insulated us from the danger of that ancient enemy, sepsis. Recently the resistant staphylococcus has appeared to plague us in breast abscesses and abdominal wounds. It behooves those of us who have seen the complete cycle diligently to re-emphasize surgical asepsis in the care of obstetric patients.

It is to be hoped that new antibiotics will be forthcoming to aid in the control of the more resistant organisms. Nothing, however, can or should substitute for vigilant surgical asepsis. It is far safer to prevent an infection than to be obliged to use heroic measures to combat it.

Editor's comment

Intrapartum infections remain a grave complication, much more so than postpartum infections. The latter have been controlled to a large extent by judicious preventative measures in the avoidance or correction of intrapartum infections, by improved obstetric care and by the use of adequate and proper antibiotics or sulfonamide preparations. Intrapartum infections are less well controlled by antibiotics and sulfonamides. With the fetus still within the uterus the situation is quite different than with the infant de-

livered. Since delivery of the infant is often required in the best interests of management, especially in case of ruptured membranes, many problems are posed in the individual cases. The problems and the responsibilities of the physician are much greater.

Intrapartum infections are often made more serious because of the fact that the early symptoms and findings may be mild, seemingly insignificant and not at all indicative of the graveness of the situation. This, in addition to the availability of and the sense of security that one may have in antibiotic therapy, may lull the physician into the belief that all is well and that watchful expectancy is sufficient. Both Consultants have indicated that this is extremely wrong, that early and prompt treatment is required, that large dosages of the proper antibiotics should be administered and that the infant should be delivered as soon as possible.

That intrapartum sepsis can progress rapidly to a fatal end after a rather benign beginning is demonstrated by this case history.

To conclude this case presentation, the autopsy findings are given:

Anatomic diagnosis. Hypertrophy of the heart (420 grams), very flabby heart muscle, myocarditis; dilatation of the right ventricle, acute; edema of the lungs with distention of the alveoli, no amniotic fluid emboli found; acute splenitis, markedly enlarged spleen, typical septic spleen, sinusoids empty, marked hemolysis; focal necrosis of the liver, liver enlarged, sinuses widened; pregnancy, full term, cephalic, undelivered, placenta attached; amnionitis; septicemia.

Bacteriological cultures. Hemolytic *Staphylococcus albus* was cultured from the uterine cavity. *Pseudomonas aeruginosa* was cultured from the placenta.

Reviews | Abstracts

Edited by

LOUIS M. HELLMAN, M.D.

Reviews of new books

Amino Acids and Peptides With Antimetabolic Activity. By G. E. W. Wolstenholme and Cecilia M. O'Connor, editors for the Ciba Foundation. 286 pages, 28 illustrations. Boston, 1958, Little, Brown & Company. \$8.75.

This volume is essentially the transactions of the Ciba Foundation Symposium held in London, England, March 18-20, 1958. On this occasion, 29 participants presented papers related to the subject of amino acids and peptides with anti-metabolic and cytotoxic properties. Although the majority of the presentations are highly technical and require advanced biochemical knowledge for interpretation, there is a considerable amount of valuable clinical information noted here and there.

Unfortunately, neither the index nor the titles serve as an aid for the reader in discovering this without plodding through a maze of chemical formulas and cellular biology.

Cancer. Edited by Ronald W. Raven. Volumes 1 to 4, 2,280 pages, 231 tables, 789 figures. London, 1958, Butterworth & Co., Ltd. \$18.00 per volume.

In *Cancer*, Ronald W. Raven has endeavored to broaden our current knowledge of cancer by synthesizing the vast experience of many authors. In Volume 1, fourteen different authorities present the varying aspects of research into the causation of this disease, beginning with the historical aspects and concluding with a consideration of the carcinogenic effect of radiation. P. R. Peacock of the Royal Beatson Memorial Hospital in Glasgow has a fascinating chapter on

carcinogenesis in which he clearly points out some of the fundamental considerations of the biology and environmental phenomena related to cancer. An understanding of the future of chemotherapy is readily obtained by the reader after perusal of J. N. Davidson's excellent section on chemical mechanisms of normal and abnormal cell division as well as A. G. Griffin's portrayal of biochemistry of cancer induction. As in the later volumes, the editor has wisely selected the subjects, and at the same time, taken care to show each in its right perspective.

In Volume 2, thirty different authors present the pathological findings of malignant tumors. Perhaps because of the limitation of space, the over-all effect is one of a rather superficial and incomplete coverage of the subject. This is particularly true of Magnus Haines' chapter on uterus, ovary, Fallopian tube, vagina, and vulva. However, G. J. Cunningham has an informative presentation on the general pathology of malignant tumors. In Volume 3, the editor, with the assistance of twenty-two contributors, covers additional pathological aspects of cancer including geography, occupation, education, and detection. This includes a very instructive discussion by Ilse Lasnitzki on cancer cells in tissue culture and an equally informative presentation of cancer mortality trends in the United States by Harold Donn.

In Volume 4, the clinical aspects of cancer are covered by twenty-nine authors. John Howkins adequately discusses the treatment of malignant tumors of the uterus and stresses the importance of a careful pretherapy assessment of the patient and the necessity of consultation be-

tween the gynecologist and radiotherapist to decide on the best method of treatment. It is interesting to note that he encourages the conservative approach to younger patients with carcinoma in situ of the cervix. This reviewer was impressed with Howkins' insistence on a fractional curettage to determine the exact site and extent of carcinoma of the endometrium because he believes a simple total hysterectomy and bilateral salpingo-oophorectomy is inadequate when there is invasion of the isthmus or endocervix. Douglas MacLeod's coverage of malignant tumors of the ovary and Fallopian tubes is very superficial as well exemplified by his coverage of chemotherapy in four lines: "Regression may occur in some of the advanced ovarian tumors with chemotherapy. For example, chlorambucil is used in doses up to 10 milligrams daily, for a period of 1 month. During this period the hemoglobin, leucocytes and platelets are checked weekly." The malignant tumors of the vulva, vagina, and female urethra are similarly presented by H. H. Francis.

Although this reviewer has pointed out several areas of weakness in the material presented in the four volumes of *Cancer*, this should not be construed as a reluctance to praise Ronald Raven and his collaborators for a very excellent contribution to medical literature. On the contrary, *Cancer* is a monumental work that can be appreciated only by the individual with the time and interest to peruse its entire contents. As Ronald Raven states in the preface, future progress may change the prominence of certain subjects covered in *Cancer*. In the interim, this shall serve as an excellent reference publication and a "strong foundation on which a superstructure can be erected in the future."

Atlas of Roentgenographic Positions. By Venita Merrill. Second edition. Volumes 1 and 2, 672 pages, illustrated. St. Louis, 1959, The C. V. Mosby Company. \$32.50 (2 volumes).

This work is a two-volume edition of the *Atlas of Roentgenographic Positions* by Venita Merrill.

Venita Merrill, until recently Educational Director of Picker X-ray Corporation, has had long experience as an x-ray technician and has sought and obtained the advice and guidance of some of the outstanding radiologists in the country while preparing these volumes. Adding the support given to her by the Picker Corporation to the good guidance she received and

her own considerable ability, she has been able to turn out an excellent guidebook for x-ray technicians and for the radiologist, too.

The books are beautifully printed and are copiously illustrated by excellent x-ray reproductions and well-drawn diagrams. The texts are readable and intelligently brief. Intentionally omitted are discussions of x-ray exposure factors, on the assumption, I suppose, that the x-ray departments determine such matters themselves. In the reviewer's opinion this omission is a weakness of the books. Apart from serving the technicians working in well regulated university departments, the books will be used by many others to whom guidance in exposure technique would be useful. This is particularly so for those technicians who are working in individual radiologists' offices and offices of non-radiologists. Also omitted from these volumes is any discussion of x-ray protection factors. The technicians constitute a very real and important part of the radiation protection team and they should be instructed in factors of radiation protection both for themselves and for the patients and the surroundings. In light of today's awareness of the hazards involved in diagnostic radiation when improperly used, no one, not even the technician, can be relieved of his share of responsibility.

All in all, these volumes are highly recommended as an atlas of the usual and even the very unusual positionings of the patient for radiographic examination.

Medical Management of the Menopause. By Minnie B. Goldberg. 88 pages, 10 figures, 5 tables. New York, 1959, Grune & Stratton, Inc. \$4.50.

A concise approach to management of the menopausal syndrome with therapy aimed toward maintaining normal physiologic function is advocated by Dr. Goldberg.

The menopausal syndrome consists of a variety of unpleasant symptoms involving any or all of the systems of the body. It results from hormonal imbalance, essentially a deficiency of estrogens. Symptoms sufficient to require therapy occur in approximately 50 per cent of women. They may appear before, coincident with, or following the cessation of menses. Therapy includes reassurance, sedation, psychotherapy, and hormonal supplementation. The first three, although helpful and necessary, do not constitute adequate treatment for any but the

mildest cases. Administration of estrogens, alone or in combination with androgens, constitutes specific therapy. The choice of preparation and the size and interval of dose, as well as the route of administration, must be determined on an individual basis. This demands careful supervision and regulation. Treatment must be cyclical, that is, interrupted by rest periods, to avoid cumulative effects. The goal of therapy is to achieve maximum relief with minimum dosage and minimum incidence of undesirable reactions.

Successful therapy of the climacteric requires patience, perseverance, and careful attention to minutiae. It demands a willingness to listen to the patient's complaints and observations with an open mind and sympathetic understanding. Further, it demands a willingness to concede that that featherless biped, woman, far from being perverse, has good reason for her complaints, even though they are on a functional basis. With such a mental approach to the problem and with the help of the great advances made by the biochemists and pharmacologists in placing effective tools at our disposal, much has been done and will continue to be done to lighten the distress common to women in the autumn of life.

Hormontherapie in der Frauenheilkunde-Grundlagen und Praxis. By Joachim Ufer. 157 pages, 66 figures. Berlin, 1959, W. de Gruyter. DM 32.

This concise but thorough review of hormone therapy in gynecology and obstetrics provides an excellent résumé of the present knowledge and uses of the endocrine hormones for the busy practitioner. The book starts with a short, clear review of the chemistry, synthesis, and degradation of the various steroid and protein hormones. The physiologic effect of each of the hormones is then discussed, including a quick historical background for each. The author then categorizes the various forms of hormones available to the therapist and the various modes of administration, including the advantages and disadvantages of each. The next section, which contains a great deal of information in its few pages, discusses the various diagnostic procedures to be used and a plan of approach to the diagnosis of endocrine disease. The various laboratory procedures available to aid in diagnosis, and the significance of the values obtained are also discussed at this point. The remainder of the book is devoted to definitive therapy

utilizing hormones and is logically divided into management of disturbances of puberty, menstrual disorders during the childbearing years, menopause, post menopause, hormone therapy of carcinoma, hormonally active tumors of ovary, adrenal and pituitary, and finally hormone therapy as an adjunct to gynecologic surgery, such as the use of cortisone preparations in surgical shock and the use of supportive hormone therapy with operations during pregnancy. At the end of the book there is a complete table listing all of the clinically available hormone preparations, their dosage and form of administration, and the commercial trade names under which they are marketed in Germany.

As a whole, the book is well written, very well organized, and very thorough in its coverage of the therapeutic uses, despite its small size. The book cannot help but express uses which might be opposed by some workers; however, it is good to see definite therapy regimes listed and doses stated in place of generalities as this provides a base from which to build and work. The book should be of value to anyone in this field who reads German.

Nutrition in Pregnancy. Symposium IV, Council on Foods and Nutrition of The American Medical Association.

Seven aspects of nutrition and their effect on gestation in man and experimental animals are discussed in this symposium. The nutritional state of the mother prior to conception appears to effect the pregnancy wastage and neonatal mortality. If the nutritional level of the mother is low, improvement of her nutrition, even late in pregnancy, improves the status of the infant. There is a great need for nutritional education of the American Public, not only infant nutrition, but also adolescent and adult nutrition as well.

Dr. Ray Halpner feels that maternal nutrition directly affects the fetus and that much of the loss of human life in the newborn period associated with the problems of reproduction, sterility and abortion, premature or immature birth and stillbirth, toxemia, and malformation can often have their origin in nutritional defects.

Mammalian experimentation has often revealed congenital multiple system lesions produced by various nutritional deficiencies. However, caution must be exercised since the animal

was subjected to artificial experimental conditions which are not likely to occur in human beings.

The Vanderbilt Cooperative Study of Maternal and Infant Nutrition reported its findings on the effect of the reproductive cycle on the nutritional status of their clinic population, concluding that there are definite alterations in the patterns of dietary intake and biochemical values during the reproductive interlude which revealed fundamental physiologic changes in the pregnant and lactating mother. They feel that adequate dietary supplementation should be applied as needed, but care should be exercised to avoid needless therapy.

Finally, many fundamental and regulating mechanisms of the body are thrown out of balance by the demands and effects of pregnancy, and these disturbances should be corrected when indicated.

Physiology of the Newborn Infant. By Clement A. Smith. Third edition. 497 pages, 62 figures, 60 tables. Springfield, Ill., 1959, Charles C Thomas, publisher. \$12.50.

Those who know Clement A. Smith cannot help but feel a bit of borrowed pride on perusing the pages of the third edition of *Physiology of the Newborn Infant*. For others who are not so fortunate as to call the author friend, the republication of this classic furnishes a unique source of information on the fetus and the newborn infant which is modern in its approach, broad in its scope, and accurate in its scholarship.

Now, as in previously published editions, this is an entirely personal work, being detailed and most exciting in the fields of the author's interest and more pedestrian in areas which do not intrigue him. Thus, the two chapters on respiration and the one on circulation are tremendous. While some of the others do not maintain such a high level, they are nevertheless sound and scholarly. This is hardly a criticism of the work for, from another point of view, the author has given proper emphasis to those areas where research is most directed and progress most evident. However, one cannot help but be amused that the promised chapter on the nervous system is still apologetically missing. It would be a good guess that until all of the problems of respiration and circulation are solved, it will not appear in future editions.

Accurate in scholarship, almost never dogmatic, essentially sound in its approach to current research, and, above all, fresh and exciting, this is a worthy successor to the previous two editions.

Recent Progress in Oxytocin Research. By B. Berde (American Lecture Series—Publication 300). 110 pages, 37 figures, 13 tables. Springfield, Ill., 1959, Charles C Thomas, publisher. \$4.75.

This small book, with but 82 pages of text, has merit but does not fulfill the promise its title suggests. It is readable for a highly technical volume. It will be of most use and interest to one interested in obstetrical physiology.

There are 6 chapters plus introductory remarks and a section on references. The first 3 chapters are on the chemistry, biologic activity, production, and fate of oxytocin. They are well done. There is heavy reliance on work with animals.

The fourth chapter, entitled "Oxytocin and Labour," is cursory and glosses over the important American work. A fifth chapter, on oxytocin and lactation, is a satisfactory summary of the topic. The sixth and final chapter, on some other actions of oxytocin, notably its effect on excretion, circulation, and electrolyte balance, completes the report.

The references are overwhelmingly to the foreign literature.

Anesthesia for Infants and Children. By Robert M. Smith. 418 pages, 182 figures. St. Louis, 1959, The C. V. Mosby Company. \$12.00.

This book is the first comprehensive review of pediatric anesthesia—all the more convincing as the author writes from a wide experience. In the opening chapters the various biological factors are discussed in relationship to the problems of anesthesia in these small patients. After a description of pediatric anesthesia equipment, the greater part of the remainder of the book is a well-written account of anesthetic management in the different ramifications of pediatric surgery. Treatment of respiratory insufficiency, oxygen therapy, and the legal aspects of pediatric anesthesia are outlined. The statistics presented show that in a well-run department the mortality associated with pediatric anesthesia need not be higher than that attendant to the use of anesthesia in the adult population.

Only anatomical reasons for endotracheal intubation are presented; yet, there are many who feel that this procedure is justified in some cases from the reduction of dead space alone—especially in prolonged procedures. The author prefers to use closed circuit techniques in many situations which, in the reviewer's opinion, could be handled adequately by nonrebreathing systems. The agents and techniques recommended in Table 13 represent the author's own point of view, though other anesthetics and methods could be used equally well.

The standard of production and readability of this book are of a high order and it contains much sound advice.

Biopsy Manual. By J. D. Hardy, J. C. Griffin, Jr., and J. A. Rodriguez. 150 pages, 54 figures. Philadelphia, 1959, W. B. Saunders Company. \$6.50.

The various aspects of biopsy are considered here, including the general principles, the complications, and the instruments employed. Each chapter is devoted to a single region or organ of the body. The methods of performing the biopsies are excellently illustrated and the descriptions are adequate. The bibliography is quite sufficient if one is interested in special information.

Portio-Karzinom. By Kurt Michalzik. 211 pages, 269 figures. Munich and Berlin, 1959, Urban and Schwarzenberg. DM 36.

Dr. Kurt Michalzik has compiled the abnormal findings in a group of 5,000 women who were examined for uterine cancer by means of cytodiagnostic, colposcopic, and histologic techniques. Basically, he attempted to correlate the findings in these 5,000 women as to their Papanicolaou smears and the colposcopic appearance. He also used the additional features of Giemsa staining of vaginal smears to advance the old hypothesis that carcinoma is a result of vaginal irritations set up by vaginal microorganisms and infections.

To emphasize his findings, he used 269 photomicrographs of his more interesting cases. Un-

fortunately, these are not in color. The quality of the photographs are first rate, however, and generally the diagnosis is justified. Through a complicated system of symbols he attempts to show the follow-up of interesting cases by grading the smears not only as to the five classes of Papanicolaou but also to eight grades of hormone activity. The numerous subdivisions of vaginitis, leukoplakia, and eventually cellular atypicality all receive symbols which, according to the author, enable him to make the diagnosis of early cancer in the suspicious smears (Classes III, IV, and V), and also to point out that the etiology of cervical carcinoma lies in vaginal irritations caused by microorganisms.

The point is mentioned that since there are no cellular elements that make a cytologic diagnosis of cancer a certainty, the technique must still be only a screening one. The author believes that vaginal microorganisms, especially *Trichomonas vaginalis* can not only simulate the most severe class of cytologic smear but actually over a period of time can produce carcinoma of the cervix. This is usually preceded by leukoplakia and it is this progressive change that can best be followed by colposcopic examination.

His general findings were these: In the 5,000 patients 28 epidermoid carcinomas of the cervix were found, 11 of which were associated with leukoplakia. In 38 additional cases classified as highly atypical 26 were trichomonas vaginitis. The author believes that by using statistical methods he can conclude that cervical epithelial atypicality is caused by trichomonas vaginitis.

The book is useful only as a basis of comparison. The concept of cold conization of the cervix on all suspicious cytologic smears after multiple biopsy to rule out invasion is not mentioned. The orderly, progressive, logical pursuit of cervical cancer as undertaken in most of our American gynecologic clinics seems to be absent in this monograph. The time spent in speculative correlations could best be spent in enlightened patient care and time-proved cancer diagnosis procedures.

Books received for review

Human Nutrition and Dietetics. By Sir Stanley Davidson, A. P. Meiklejohn, and R. Passmore. 844 pages, 24 plates, 55 figures, 57 tables. Baltimore, 1959, Williams & Wilkins Company. \$15.00.

Pain and Itch—Nervous Mechanisms. By G. E. W. Wolstenholme and Maeve O'Connor, editors for Ciba Foundation Study Group No. 1. 120 pages, 41 illustrations. Boston, 1959, Little, Brown & Company.

Physician and the Law. By Rowland H. Long. Second edition. 302 pages, 9 tables. New York, 1959, Appleton-Century-Crofts, Inc. \$5.95.

Psychological Appraisal of Children With Cerebral Defects. By Edith Meyer Taylor. 499 pages, 16 figures, 12 tables. Cambridge, 1959, Harvard University Press. \$8.50.

Röntgendiagnostik beim Neugeborenen und Säugling. By Hermann G. Wolf. 317 pages,

370 figures. Vienna, 1959, Wilhelm Maudrich Verlag. \$23.60.

Steric Course of Microbiological Reactions. By G. E. W. Wolstenholme and Cecilia M. O'Connor, editors for Ciba Foundation Study Group No. 2. 115 pages, 37 illustrations. Boston, 1959, Little, Brown & Company.

Surgical Forum—44th Clinical Congress, 1958, Volume 9. By Harris B. Shumacker, Jr., Chairman. 866 pages, illustrated. Chicago, 1959, American College of Surgeons.

Synopsis of Gynecology. By Robert James Crossen, Daniel Winston Beacham, and Woodard Davis Beacham. Fifth edition. 340 pages, 106 figures. St. Louis, 1959, The C. V. Mosby Company. \$6.50.

Textbook of Surgical Physiology. By R. Ainslie Jamieson and Andrew W. Kay. 623 pages, 13 tables. Baltimore, 1959, Williams & Wilkins Company. \$11.00.

Selected abstracts

Acta obstetricia et gynecologica scandinavica

Vol. 38, 1959

*Engstrom, L., and Wqvist, N.: The Effect of Relaxin on the Duration of Labor Induced by Oxytocin, p. 172.

*Unnéus, C. E.: Heart Volume and Prematurity, p. 340.

Engstrom and Wqvist: Effect of Relaxin on Duration of Labor Induced by Oxytocin, p. 172.

The series investigated comprised 130 multiparas at or near term in whom labor was induced by infusion of oxytocin, the most frequent indication being Rh-sensitization. Thirty patients were given relaxin (Releasin) and oxytocin (Syntocinon), and 100 received oxytocin alone. The latter cases were used as controls. The aim was to study the effect of relaxin on the duration of the different stages of labor.

The duration of the latent phase in the group

in which the relaxin-oxytocin combination was used was 4.93 hours and in the controls 3.01 hours, the difference being highly significant. Moreover, in the oxytocin group a smaller quantity of oxytocin solution was required. The patients treated with relaxin and oxytocin were given 695 ml. and the controls 516 ml. of oxytocin solution; the difference is statistically significant and is an objective measurement of the variation between the two groups in respect to the quantity of oxytocin required. It is interesting to note, however, that the incidence of successful induction was higher in the relaxin-oxytocin group despite prolongation of the latent phase. In the present series, induction of unselected cases was successful in 90 per cent of the patients to whom oxytocin was administered and in 97 per cent of those receiving oxytocin combined with relaxin. The fetus presented by the head and was alive at the time of commencement of the oxytocin drip in all cases.

The durations of the different stages of labor in both the group treated with oxytocin supple-

*These articles have been abstracted.

mented by relaxin and the group given oxytocin alone were studied. There was no significant difference between the two groups in respect to the duration of the first and second stages of labor. A shortening of the second stage was suggested in the group treated with relaxin and oxytocin, but the difference was not statistically significant.

Robert E. L. Nesbitt, Jr.

Unnérus: Heart Volume and Prematurity, p. 340.

At present approximately two thirds of the neonatal mortality is attributable to the consequences of prematurity. Of the fetal deaths, about 50 per cent are in premature infants. Since 1955, the author has conducted an extensive investigation concerning the relationship between the heart volume of the mother, the birth weight of the infant, and the frequency of prematurity. From a frontal x-ray picture, measurements were taken of the horizontal and vertical axes, the product of which was then multiplied by the value for the length of the sagittal horizontal axis measured from a lateral picture. The result was then multiplied by a known factor in order to eliminate the magnification due to the divergence of the x-rays. Examination of volume variations in exposures made at different cardiac phases showed that this source of error was insignificant. Making the exposure immediately after the patient completed a moderate inspiration obviated the Valsalva effect which might result in too low a value for the heart volume. In practice, errors exceeding 3 to 4 mm. did not generally occur in measuring. The error in the volumes calculated from the diameters was 10 c.c. It is known that cardiac efficiency can be determined by other techniques, but the author believes that radiology is the most effective.

In about two thirds of the pregnancies resulting in premature delivery, the heart volume of the mother was below 600 c.c. In the pregnancies resulting in full-term deliveries, only one third of the mothers had a heart volume below 600 c.c. The percentage risk of premature deliveries decreased by 50 per cent for every increase of 100 c.c. in the heart volume. Also, a good correlation was noted between the weight of the infant and the maternal heart volume the day after parturition, regardless of the duration of the pregnancy.

A heart volume of 320 c.c. per square meter of body surface is a value which makes it necessary to subject the patient to special supervision. The

investigations showed distinctly that in heart volume and hemoglobin per cent, one has a relatively simple and reliable method of reducing the number of premature births. It proved possible by means of prenatal care to advise pregnant women to take more rest toward the end of pregnancy. A series of 804 deliveries included 90 women who had been advised to rest because of a small-sized heart. The expected ratio of premature births among them would have been 1:7, i.e., around the usual incidence. Instead there was only one case of prematurity. In the group of women for whom rest was not prescribed, the size of the heart showed diminution among those who were delivered prematurely. This observation was especially true of deliveries occurring in the spring, which suggested to the author that diet can be regarded as playing an essential role in the matter.

Robert E. L. Nesbitt, Jr.

Anesthesiology

Vol. 20, September—October, 1959.

*Ichiyangi, Kunio, and Morris, Lucien E.: Effect of Cyclopropane and Various Oxytocics on Cardiac Rhythm in the Parturient Woman, p. 669.

Ichiyangi and Morris: Effect of Cyclopropane and Various Oxytocics on Cardiac Rhythm in the Parturient Woman, p. 669.

In a series of 72 patients, the authors have shown no significantly greater incidence, by electrocardiograph, of cardiac rhythm irregularities associated with the intravenous addition of Pitocin or Syntocinon, a synthetic oxytocic, to a patient anesthetized with cyclopropane. They specifically excluded all cases in which any degree of hypoxia was noted and attempted to maintain anesthesia in the first plane of the third stage, by clinical signs, to keep the number of irregularities to a minimum.

They express a preference for the synthetic oxytocic to the natural only to the extent that it is not liable to be contaminated with any pituitary pressor fraction and cause the untoward results reported with the use of this agent.

Abraham Lenobel

British Medical Journal

Vol. 1, May 23, 1959.

*Aird, Ian: Conjoined Twins—Further Observations, p. 1313.

*Bailey, J. P., Hutchinson-Smith, B. H., Barber, M., and Dunsford, I.: Immunization During Pregnancy to the Kidd (JK^a) Red-Cell Antigen, p. 1329.

*Agnew, Alec M.: Surgery in the Alleviation of Dyspareunia, p. 1510.

*Oestrogen Sensitivity of the Female Urethra, p. 1518.

Aird: Conjoined Twins, p. 1313.

The author discusses 3 sets of living conjoined twins and 4 stillborn pairs of conjoined twins.

The arguments for a monovular origin for the large majority of conjoined twins are presented. The grounds for this belief are as follows: (1) conjoined twins nearly always unite at nearly identical parts of their external surfaces; (2) conjoined twins are nearly always of the same sex; (3) there is a very low incidence of twinning in the family, hence nearly excluding a binovular origin.

It is suggested that conjunction may really be due to the union of binovular germinal areas and the following circumstances may support this point: (1) conjoined twins are not identical in the same degree as separate uniovular twins; differences of feature, stature, and temperament are nearly always detected; (2) conjunction of extensive degree is very commonly associated with asymmetry in the internal organs; (3) endocrine asymmetry sometimes occurs.

It is suggested that chimerism should be sought in conjoined twins. The demonstration of a chimera would very strongly suggest an origin from two separate ova.

John J. Dettling

Bailey et al.: Immunization During Pregnancy to the Kidd (JK^a) Red-Cell Antigen, p. 1329.

A case is reported in which anti-JK^a was present as well as the rhesus antibodies anti-C and anti-D. The only stimulus was pregnancy. The production of anti-JK^a as a result of pregnancy is rare.

The anti-JK^a was in the nongamma fraction, and unless the antoglobulin serum used had antibodies against globulins other than gamma globulins, the anti-JK^a could not be detected.

The presence of complement enhanced the reactions of the antibody. Similar experiences have been found with anti-K, anti-Le^a, and anti-Fy^a, and have demonstrated the importance of using fresh serum for compatibility tests and of using antiglobulin serum capable of detecting the non-gamma globulin-type antibodies.

John J. Dettling

Agnew: Surgery in the Alleviation of Dyspareunia, p. 1510.

The author summarizes those conditions in which surgery may provide the sole answer in relieving dyspareunia, which he then divides into those of acquired and those of congenital origin.

The congenital types, consisting of (A) the thickened, undilatable hymen; (B) vaginal septa; (C) hypoplasia of the introitus, are mentioned, along with the various surgical approaches.

The acquired causes include: conditions resulting from overzealous gynecologic operation resulting in the need for secondary operation to relieve the complicating symptoms; the rare incidence of dyspareunia secondary to retroversion and its relief by operation; the role of endometriosis in producing this symptom and its amelioration by operation; and last, the part that chronic infection, chiefly pelvic inflammatory disease and chronic cervicitis, may play in the production of dyspareunia, with the review of the surgical approaches to those conditions.

In summary, he suggests that these conditions should always be ruled out in the patient who presents with what might otherwise be considered a marked emotional disturbance.

Stuart O. Silverberg

Oestrogen Sensitivity of the Female Urethra, p. 1518.

Progressing from the hypothesis that since the distal two thirds of the urethra develops from the urogenital sinus and is lined by epithelium of "sinus," it should respond to the cyclic variations of ovarian hormones; several workers have studied urinary sediment as a source of cells to demonstrate estrogenic effect.

These workers have successfully shown a definite correlation between cellular morphology and the estrogen stimulus. The cytology appears to differ in one important respect to that of the vagina. In addition to basal and cornified cells, in the same proportions and categories as in the vagina, the centrifuged sediment of female urine was found to contain a peculiar coarsely granular nonnucleated cell remnant to which some workers have ascribed particular significance, as they are found in greater numbers after x-ray castration and in postmenopausal women. They feel that these cell remnants may be associated with a response to estrogens derived from the adrenal cortex.

Further studies in women with breast cancer showed that the number of these cells, which is

low in premenopausal women, rose sharply following oophorectomy and fell abruptly again following hypophysectomy.

The significance of these findings, when and if confirmed, are discussed, and the suggestion that this method could obviously be adapted to routine clinical investigation is discussed and further work along this vein encouraged.

Stuart O. Silverberg

Cancer Research

Vol. 19, August, 1959.

*Nadkarni, M. V., Trams, E. G., and Smith, P. K.: Preliminary Studies on the Distribution and Fate of TEM, TEPA, and Myleran in the Human, p. 713.

Nadkarni, Trams, and Smith: Preliminary Studies on Distribution and Fate of TEM, TEPA, and Myleran in the Human, p. 713.

With the increasing use of the alkylating agents in the chemotherapy of cancer, the authors thought it pertinent to study the distribution, metabolic alterations, and excretory fate of these agents following administration to cancer patients. The purpose of the study was to measure concentrations in blood, rates of disappearance, and the urinary excretion following drug administration. A comparison of the excretory patterns following an oral as against an intravenous administration was made.

Radioisotopic tracer techniques were employed, the isotopic element being present in the "carrier" portion of the drug in TEPA-P³² and Myleran-S³⁵, and in the alkylating portion in Myleran-C¹⁴ and TEM-C¹⁴. The drugs were administered individually to 12 cancer patients. All drugs disappeared rapidly from the blood after intravenous administration. Between 90 and 95 per cent of the drug was removed from the circulation within 3 to 5 minutes after injection. After this initial fall, however, a level of 1 to 3 per cent of the injected dose was maintained for the 48 hour period of observation. Maintenance of relatively high blood levels appeared impossible to achieve. Following oral administration an initial lag of 1½ to 2 hours was observed before measurable blood levels would be obtained. However, at periods longer than 4 hours, the circulating activity was comparable to that obtained by the intravenous route.

None of the drugs was excreted unchanged in the urine.

The studies indicated a common pattern of metabolism of alkylating drugs in the human. A study of urinary metabolites of each drug suggested detachment of the alkylating moiety from the "carrier" portion of the drug molecule.

Richard Calame

October, 1959.

*Toplin, Irving: A Tissue Culture Cytotoxicity Test for Large-Scale Cancer Chemotherapy Screening, p. 959.

Toplin: Tissue Culture Cytotoxicity Test for Large-Scale Cancer Chemotherapy Screening, p. 959.

The author describes a tissue culture technique for testing the antitumor activity of new agents. The test includes three essential steps:

1. Dispensing of graded doses of test solution directly into disposable plastic containers by a microbuilt technique.

2. Addition of a HeLa or other human cell suspension standardized at 10,000 to 15,000 cells per milliliter in growth medium to a total volume of 1 ml. per container.

3. Microscopic evaluation of cytotoxicity after 5 days' incubation of a prescribed cytotoxicity rating system.

For microscopic evaluation of cell damage, an arbitrary scale of increasing cytotoxicity based on morphological characteristics was employed. Two end points were also determined for each assay: a cytotoxic end point and a lethal end point.

The report includes results obtained with some newer compounds, and some compounds of known antitumor activity.

The test is a simple, rapid, and relatively inexpensive method for large-scale cancer chemotherapy screening.

Richard J. Calame

Federation Proceedings

Vol. 18, 1959.

*Huckabee, W., Metcalf, J., Prystowsky, H., Hellegers, A., Meschia, G., and Barron, D.: Uterine Blood Flow and Metabolism in Pregnant Sheep at High Altitude, p. 72.

*Meschia, G., Prystowsky, H., Hellegers, A., Metcalf, J., Huckabee, W., and Barron, D.: The Oxygen Dissociation Curves of the Bloods of Adult and Fetal Llamas, p. 104.

*Metcalf, J., Meschia, G., Hellegers, A., Prystow-

sky, H., Huckabee, W., and Barron, D.: Transfer of Oxygen Across the Sheep Placenta at High Altitude, p. 104.

Huckabee et al.: Uterine Blood Flow and Metabolism in Pregnant Sheep at High Altitude, p. 72.

Pregnant sheep at 40 to 130 days of gestation were studied at sea level and at an altitude of 15,000 feet (Morococha, Peru). The high altitude sheep spent their lives at that altitude. Rate of uterine blood flow was measured in both groups by the 4-amino antipyrine method previously described. Arterial and uterine venous blood samples were obtained through small catheters placed in the vessels 24 hours prior to sampling. All animals were unanesthetized and standing quietly. In the high altitude group, 73 blood flow determinations were carried out on 17 animals; at sea level 55 on 17 animals. Hypoxemia of altitude (average P_{aO_2} 45 mm. Hg), with acclimatization of the type described, was associated with a moderate but significant increase in rate of blood flow through the uterus per kilogram of tissue. No effect of gestational age was noted. The altitude changes averaged 35 per cent. Rate of consumption of O_2 by the tissues, however, was the same at high altitude as at sea level (10.8 ml. per kilogram per minute at Morococha and 10.5 ml. per kilogram per minute at sea level). Tissue oxygen consumption and CO_2 production rose steadily as pregnancy progressed and then fell slightly near term. Prior to 90 days of pregnancy, during rapid placental growth, the RQ of the fetus was higher than that of the whole pregnant uterus in every case; afterwards, during rapid fetal growth, the reverse was found.

Meschia et al.: Oxygen Dissociation Curves of Bloods of Adult and Fetal Llamas, p. 104.

The O_2 dissociation curves of the bloods of 4 pregnant llamas that were living at about 15,000 feet altitude, have been studied at the Institute of Andrean Biology. In agreement with the earlier studies of Dill and associates, it was

found that the adult llama blood has a high affinity for O_2 in comparison with the blood of other mammals (at pH 7.4 is half saturated when exposed to and O_2 pressure of circa 21.5 mm. Hg). The O_2 dissociation curves of 3 fetal llamas were also determined. At equal pH values, the affinity for O_2 of the fetal llama blood is slightly higher than that of the maternal (half saturated at pH 7.4 with an O_2 pressure of circa 18 mm. Hg) and comparable to that of fetal bloods from other species. The fetal and maternal curves have been used to calculate the concentration gradient of O_2 across the epitheliochorial placenta of the llama. Such a gradient has been compared with previously determined gradients across the syndesmochorial placenta of sheep and goats and the hemochorial placenta of man and rabbit.

Metcalf et al.: Transfer of Oxygen Across Sheep Placenta at High Altitude, p. 104.

Thirty-six ewes which had been born and raised at high altitude were bred on known dates and studied at the Institute of Andrean Biology at 15,000 feet altitude. Samples of maternal arterial and uterine venous blood and fetal umbilical arterial and venous blood were taken anaerobically with the mother under spinal anesthesia. The data so obtained when compared with findings at sea level suggest a pattern of compensations, both maternal and fetal, to the alveolar hypoxia of altitude. There is a higher hemoglobin concentration, in both fetal and maternal blood at high altitudes. Despite this, the maternal arterial blood contains less oxygen due to its lower saturation (69 verses 89 per cent). The uterine venous blood, however, contains more oxygen (at a slightly lower saturation) at high altitudes than at sea level, resulting in a decreased arteriovenous oxygen difference across the pregnant uterus and a lower mean percentage saturation of maternal blood in the uterus. The umbilical venous blood, however, is as well saturated with oxygen by its passage through the uterus at high altitude as at sea level.

Items

American Board of Obstetrics and Gynecology

The next scheduled examinations (Part II), oral and clinical, for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from April 11 through 16, 1960. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I Examinations will be notified of their eligibility for the Part II Examinations as soon as possible.

The deadline date for the receipt of New and Reopened Applications for the 1961 examinations is Aug. 1, 1960. Candidates are urged to submit their applications as soon as possible before that time.

*Robert L. Faulkner, M.D., Secretary
2105 Adelbert Road
Cleveland 6, Ohio*

Symposium on uterine implantation of ova

A symposium devoted to the uterine implantation of ova, in mammals and in the human being, will be held in Brussels, Belgium, from June 24 to 26, 1960.

Lecturers include: G. Mayer (Bordeaux), M. Shelesnyak (Israel), B. Böving (Baltimore), C. Lutwak-Mann (Cambridge), E. C. Amoroso (London), E. Ramsey (Baltimore), A. T. Hertig (Boston), R. Moricard (Paris), H. Hamperl (Bonn), S. Aschheim (Paris), G. I. M. Swyer (London), and others.

All interested persons are invited to attend.

Detailed information may be obtained from J. Ferin, M.D., 42, Beukenlaan, Heverlee-Louvain, Belgium.

Foundation Prize of the American Association of Obstetricians and Gynecologists

Manuscripts of not more than 5,000 words, in three copies, under a nom de plume, the real name of the author in a separate sealed envelope, must be in the hands of Dr. Jean Paul Pratt, Henry Ford Hospital, Detroit, Michigan, before April 1, 1960.

Those eligible for this \$500 prize include (a) interns, residents, or graduate students in obstetrics and gynecology, and (b) persons with an M.D. degree, or a scientific degree approved by the Prize Award Committee, who are actively practicing, teaching, or engaged in research in obstetrics and gynecology.



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Both are basic for relief and correction of constipation

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relieves both stiffness and pain with safety...sustained effect

NOTABLE SAFETY—unusually low toxicity; no known contraindications: side effects are rare; drowsiness may occur, usually at higher dosage.

RAPID ACTION—starts to act quickly.

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Supplied
as white, coated, 350 mg.
tablets, bottles of 50. Also
available for pediatric use:
250 mg. orange capsules,
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Hard to imagine it now, but only a few years ago the Dolans were resigned to the fate of a childless couple. After four successive spontaneous abortions, the mother's chances of delivering a viable infant were discouragingly slim.

Capillary protection made the difference. To the existing prenatal regimen, her physician then added antihemorrhagic factors...Mrs. D.

attempted one more pregnancy and, this time, she succeeded perfectly.¹ Fetal salvage rates as high as 95 per cent have been achieved

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child
who*

'couldn't'

*be
born*

when hesperidin complex and ascorbic acid (as provided by Hesper-C Prenatal) were administered with the usual vitamin and mineral supplementation.²

A precaution in every pregnancy. Since 10 to 20 per cent of all pregnancies do not go to term, it is important to prevent decidual

bleeding on a routine basis. The difference in cost is insignificant; the

difference in human happiness may be incalculable.

Supplied: Bottles of 100 and 500 capsules.

1. Greenblatt, R. B.: *Obst. & Gynec.* 2:530, 1953. 2. Javert, C.: *Obst. & Gynec.* 3:420, 1954.

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THIS NEW ANORECTIC does more than give you dextro-amphetamine to curb your patient's appetite. It also gives you Miltown to relieve the tensions of dieting which undermine her will power.

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1. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.

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100 cc. contains: 16 Gm. sodium biphosphate and 6 Gm. sodium phosphate in 4½-fl.oz. squeeze bottle.

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Also available: Fleet Oil Retention Enema, 4¼-fl.oz. ready-to-use unit containing Mineral Oil U.S.P.

1. Roscnfield, H. H., et al.: *Obst. & Gynec.* 11:222, 1958. 2. Bookmiller, M. M., and Bowen, G. L.: *Textbook of Obstetrics and Obstetric Nursing*, ed. 3, Philadelphia, Saunders, 1958, p. 314. 3. Hellman, L. D.: *Gastroenterology*.

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March, 1960

Page 103

In female urethritis age makes a difference

BEFORE THE MENOPAUSE.

localized urethral infection is highly prevalent but "easily overlooked" because pain and discomfort are frequently referred to other areas.¹

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are antibacterial...anesthetic...gently dilating...provide rapid control of both pain and infection²...0.2% Furacin and 2% dipherodon-HCl (an efficient local anesthetic), in a water-dispersible base. Each hermetically sealed in silver foil, box of 12.

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estrogen deficiency leads to atrophy of the urethral mucosa, irritation, increased susceptibility to infection...a frequent source of pelvic distress.³

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are estrogenic as well as antibacterial, anesthetic and gently dilating... provide "progressive histologic normalization" and prompt symptomatic relief⁴... 0.2% Furacin, 2% dipherodon-HCl, and 0.0077% (0.1 mg.) diethylstilbestrol, in a water-dispersible base. Each hermetically sealed in orchid foil, box of 12.

REFERENCES: 1. Barrett, M. E.: J. M. Assoc. Alabama 26:144, 1956. 2. Youngblood, V. H.: J. Urol., Balt., 70:926, 1953. 3. Youngblood, V. H.; Tomlin, E. M.; Williams, J. O. and Kimmelstiel, P.: Tr. Southeast. Sect. Am. Urol. Assoc., Atlanta, Ga. (Apr. 7-11) 1957, p. 40-43. 4. Youngblood, V. H.; Tomlin, E. M. and Davis, J. B.: J. Urol., Balt., 78:150, 1957.

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94 to 6 BONADOXIN® stops morning sickness

When she asks "Doctor, what will it be?" you can either flip a coin or point out that 51.25% births are male.¹ But when she mentions morning sickness, your course is clear: BONADOXIN.

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BONADOXIN—DROPS and Tablets—are also effective in infant colic, motion sickness, labyrinthitis, Meniere's syndrome and for relieving the nausea and vomiting associated with anesthesia and radiation sickness. See PDR p. 795.

1. Projection from Vital Statistics, U.S. Government Dept. HEW, Vol. 48, No. 14, 1958, p. 398.

2. Modell, W.: *Drugs of Choice 1958-1959*, St. Louis, C. V. Mosby Company, 1958, p. 347.



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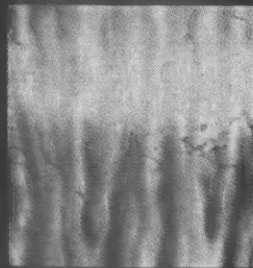
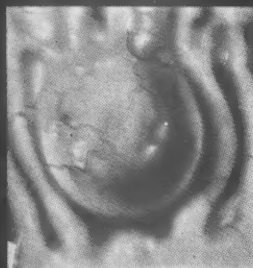
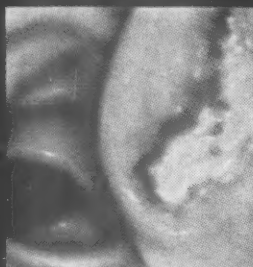
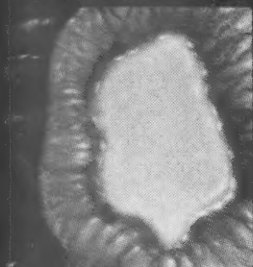


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**Schneider, H.C.: In Press, J. Intern. Coll. Surgeons*

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a prenatal supplement especially for the multipara†

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*Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.

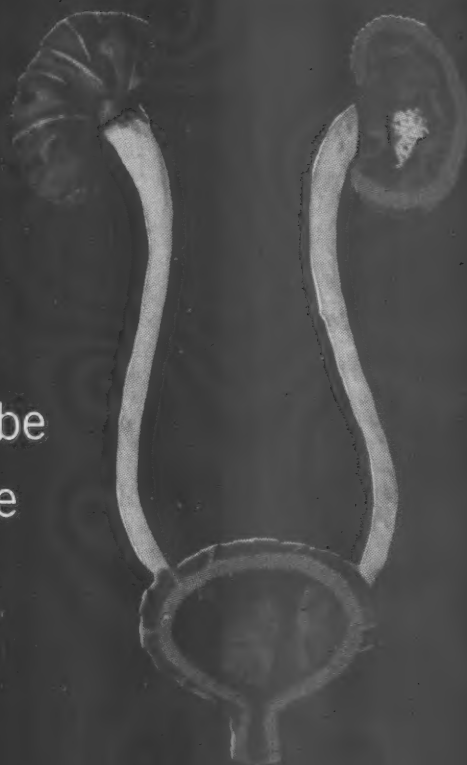
†Projected estimate from data of U.S. Office of Vital Statistics indicated that 3 out of 4 births in 1958 were to multiparas.



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REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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1. Johnson, J. F.: Paper presented at Symposium on Blood, Wayne State University, Detroit, Michigan, Jan. 18, 1957; cited in *M. Science* 1:33 (Mar. 25) 1957; *Proc. Soc. Exper. Biol. & Med.* 94: (Jan.) 1957. 2. Published and unpublished case reports, Ayerst Laboratories. 3. Rigg, J. P.: *Digest Ophth. & Otolaryng.* 20: (Nov.) 1957. 4. Rigual, R.: *Ibid.*, p. 3. 5. Servoss, H. M., and Shapiro, F.: *Ibid.*, p. 10. 6. Menger, H. C.: *J.A.M.A.* 159:546 (Oct. 8) 1957.

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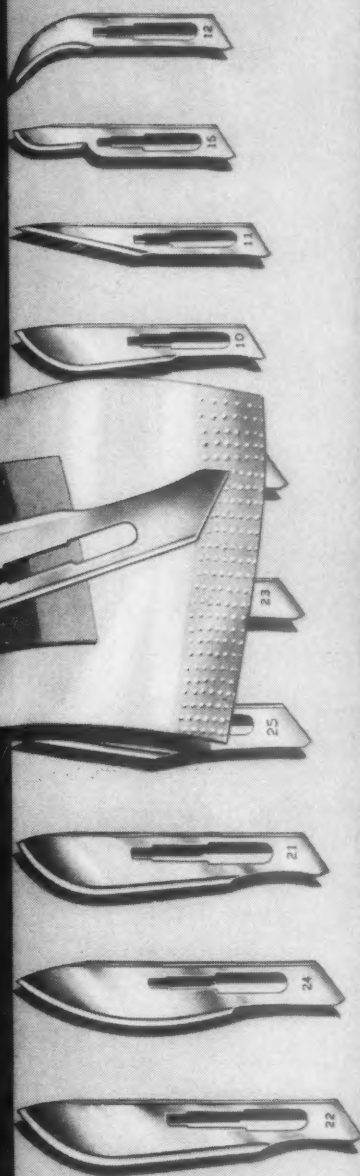
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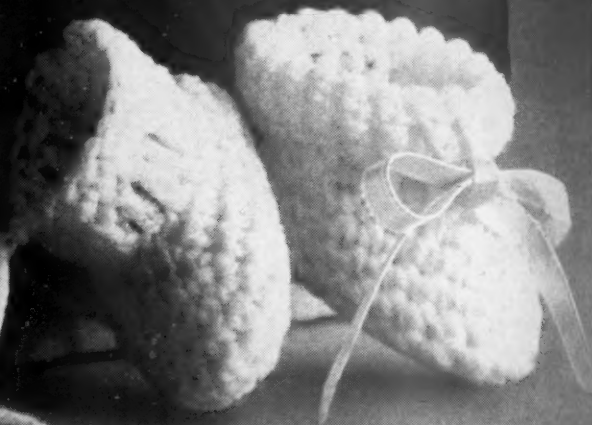
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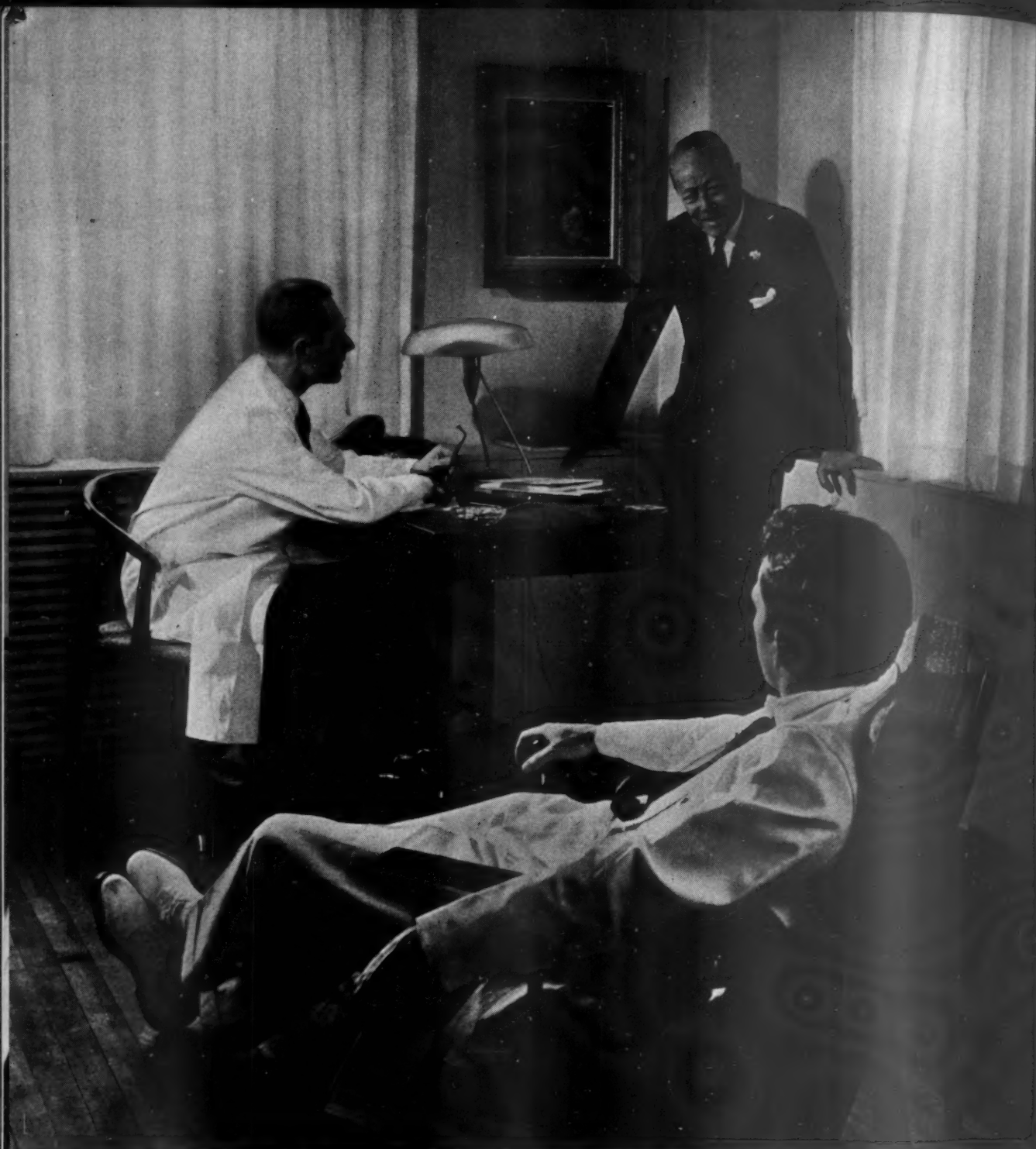
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*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1959, p. 661.



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case profile no. 3347* A 35-year-old housewife had a history of severe dysmenorrhea and premenstrual tension: Menarche, age 14; gravida II, Para I; menstrual cycle, fairly regular; pelvic examination, essentially negative results. The patient suffered from severe tension and irritability for from two to seven days before and during menstruation. Cramps were experienced during all three days of the menstrual periods. The analgesics provided limited symptomatic relief.

Trancopal, 200 mg. t.i.d., was prescribed for the dysmenorrhea. Result: Relief of severe cramping and accompanying irritability. Because of these excellent results Trancopal was prescribed for premenstrual tension. Result: Excellent response. This patient has remained on the above regimen for more than six months and no adverse effects have been noted.

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Dosage: 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

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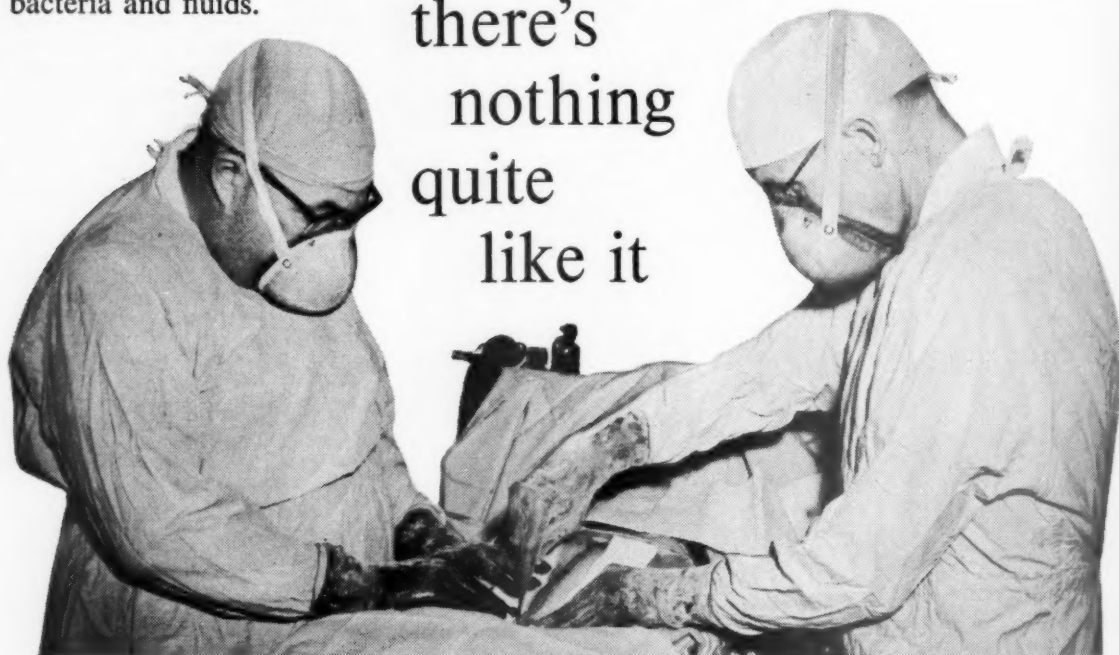
*Clinical Report on file at the Department of Medical Research, Winthrop Laboratories.

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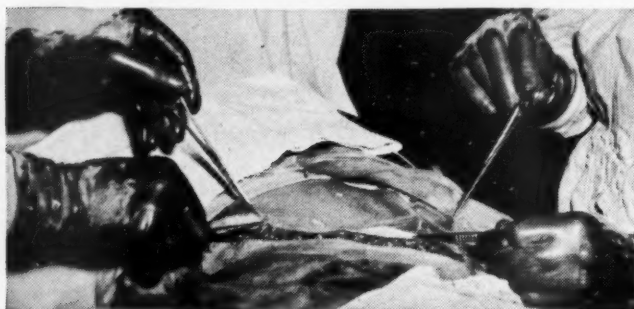
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Incise right through the Vi-Drape Film. Wider field of visibility facilitates identification of landmarks. Extensive sterile field is maintained for second incisions or double approach. For example—in bilateral herniorrhaphy incisions, the large linen drape can be shifted without fear of contamination. In inguinal hernia and orchidopexy, the scrotum remains visible and accessible

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Basic technic When freshly "prepped" skin is dry, Vi-Hesive Adherent is sprayed on to an even pink tint from about 12" distance. Sterilized Vi-Drape Film is held taut over proposed operative area then smoothly molded by hand to site and wide adjacent skin area. Photo courtesy Ralph Adams, M.D.

Sealing off the contaminated colostomy or ileostomy, and yet having it visible while exploring a new operative field, is made possible by the application of Vi-Drape Film to the entire area. Photo courtesy of Robert M. Zollinger, M.D., William G. Pace, M.D. and Marjorie N. Reed, R.N., Columbus, Ohio

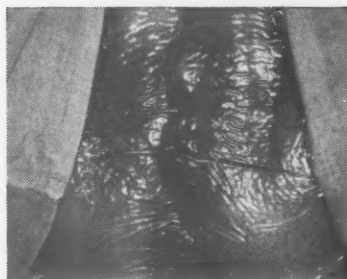
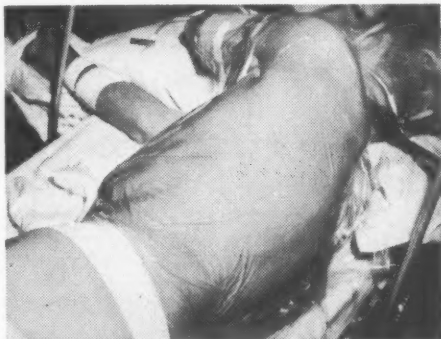


Visibility of landmarks, maintenance of asepsis in operative areas previously hard-to-drape, and isolation of the entire operative zone are particular surgical advantages of using Vi-Drape Film in neurosurgery. Illustrative is the draping of the cervical occipital area for laminectomy shown above. Photo courtesy Arthur B. Eisenbrey, M.D., Detroit, Mich.



Smooth molding and close adherence of the plastic skin drape to the difficult contour of the hip, provides an aseptic operative area previously considered almost impossible to achieve. Vi-Drape Film clings closely to the skin throughout long procedures. Photo courtesy Chas. G. Lovingood, M.D., Frank L. Shively, Jr., M.D. and Albert M. Storrs, M.D., Dayton, Ohio

Large areas can be sealed off for thoracic or cardiovascular surgery without hiding landmarks. Neck and shoulders are completely isolated from the incision. A cleaner, drier operative field is possible using plastic skin drapes. When Aeroplast Surgical Dressing is used postoperatively, evaluation of healing can be made without removing dressings. Photo courtesy Curtis P. Artz, M.D., Jackson, Miss.



Isolation of the anal area from the vaginal orifice during correction of prolapse of the vaginal vault avoids contamination by fecal extrusions.

Exteriorized vaginal vault is protected from contamination by plastic drape clinging closely to vaginal orifice during procedure and by isolation of the anus. Photos courtesy C. Paul Hodgkinson, M.D., Detroit, Mich.



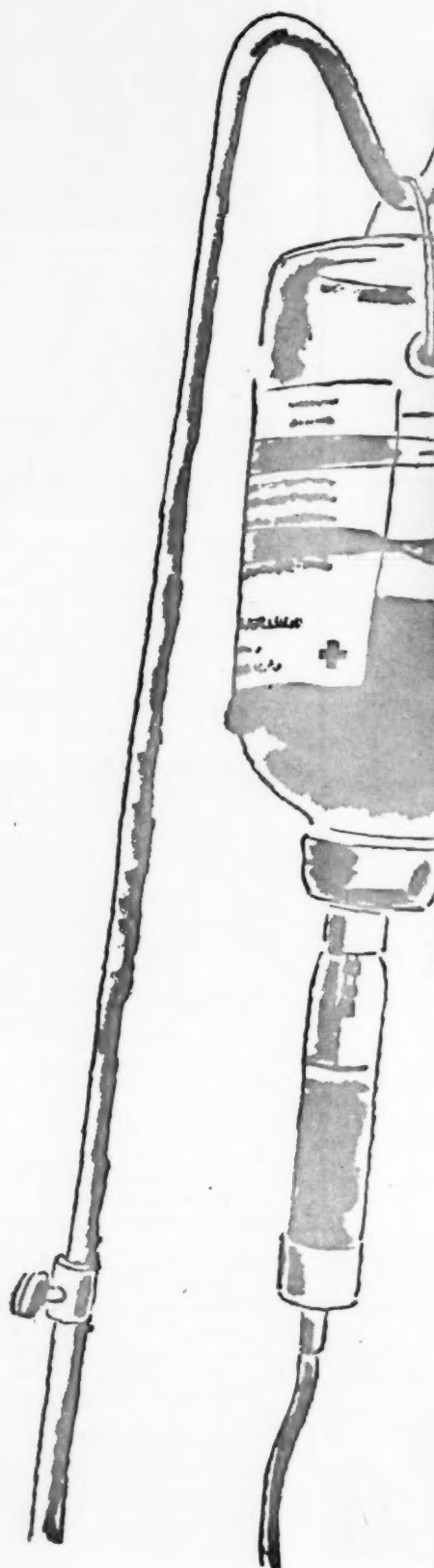
To prevent trauma, desiccation and infection — Vi-Drape Film is frequently used as a protective wrap for exposed organs as shown above holding intestines during an aortic graft. Photo courtesy Chas. G. Lovingood, M.D., Frank L. Shively, Jr., M.D. and Albert M. Storrs, M.D., Dayton, Ohio

Would you like to see a full-color sound motion picture further illustrating the application of Vi-Drape Film in varied surgical procedures? The film, "A New Transparent Plastic Surgical Drape," produced by Robert M. Zollinger, M.D., William G. Pace, M.D. and Marjorie J. Reed, R.N., at Ohio State University Department of Surgery, is available for showing to all members of the surgical team.

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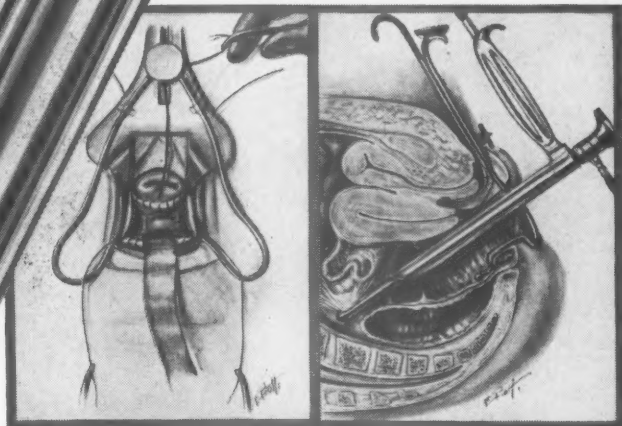
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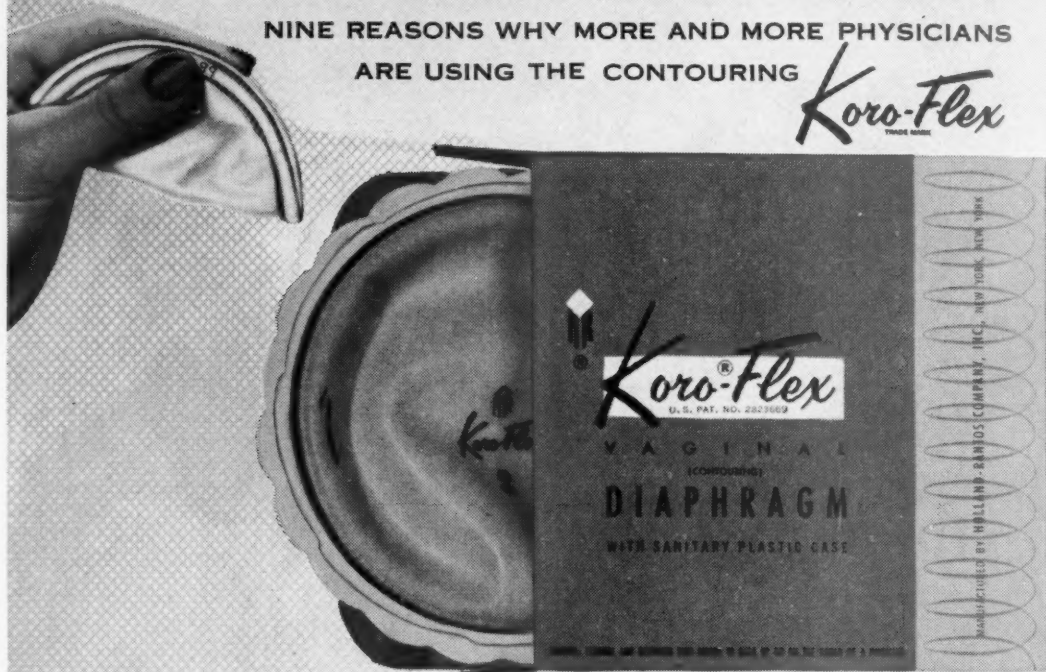


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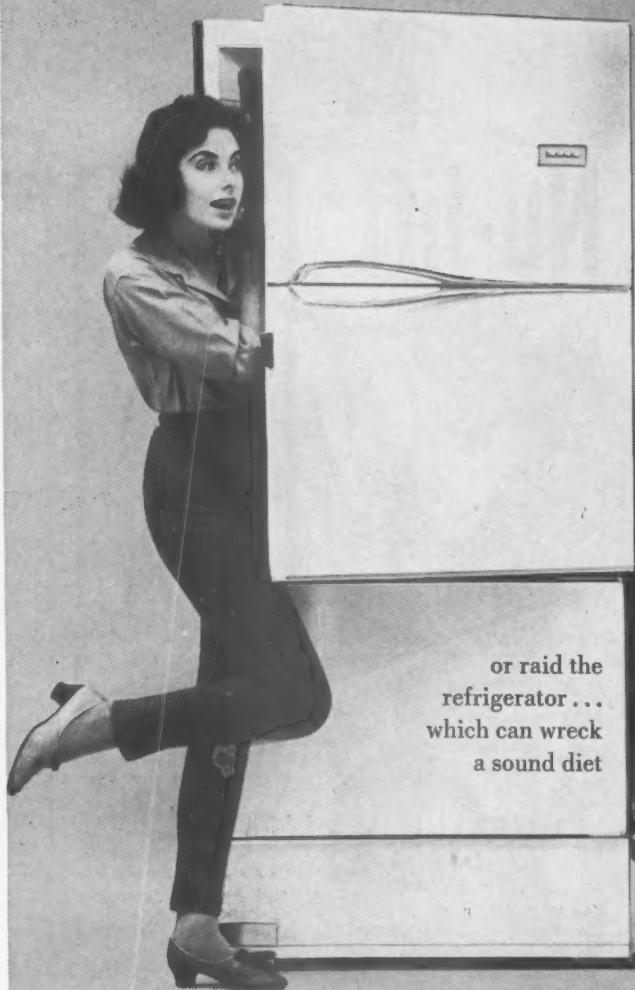


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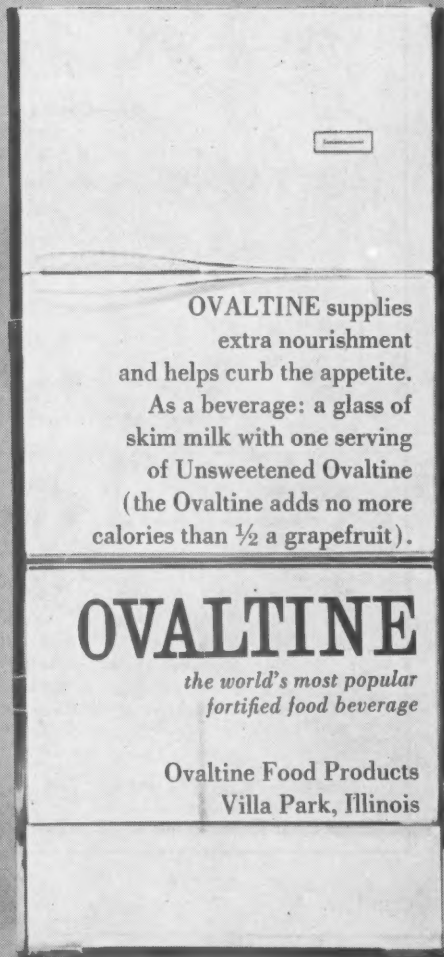
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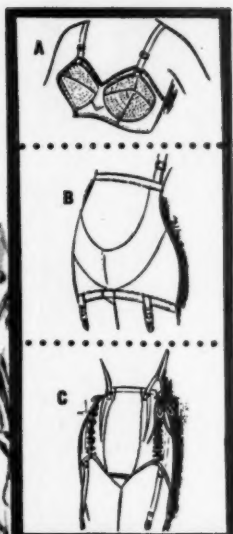
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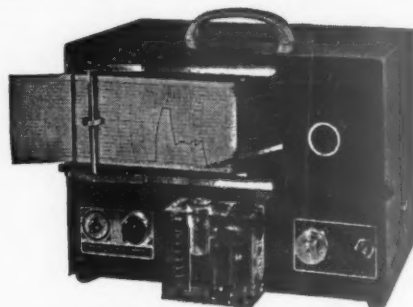
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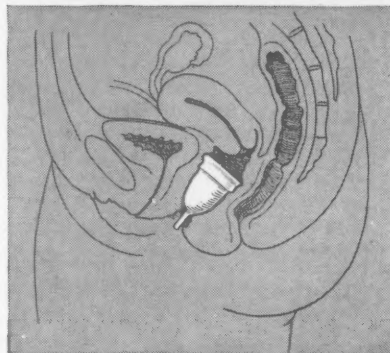
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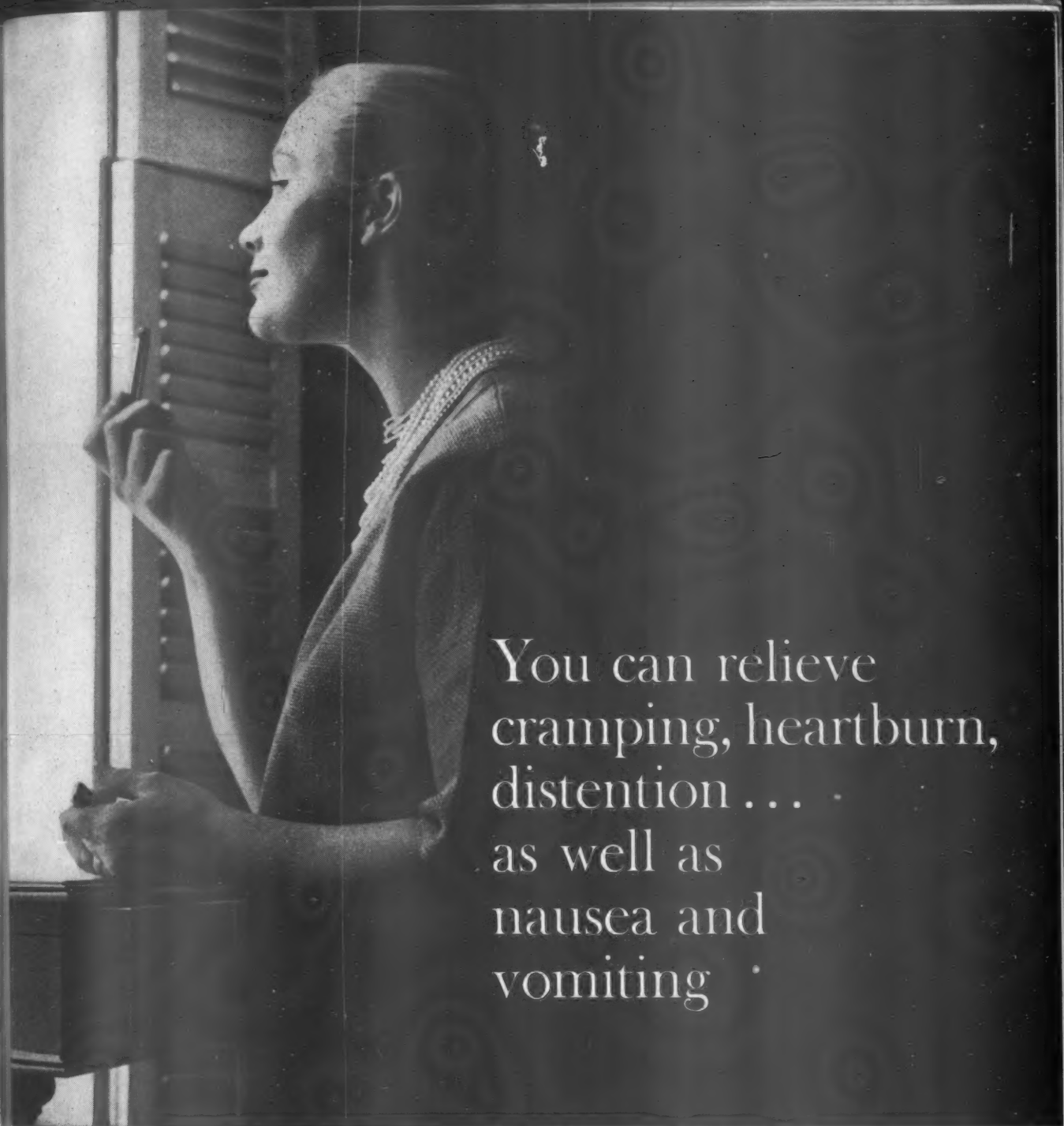
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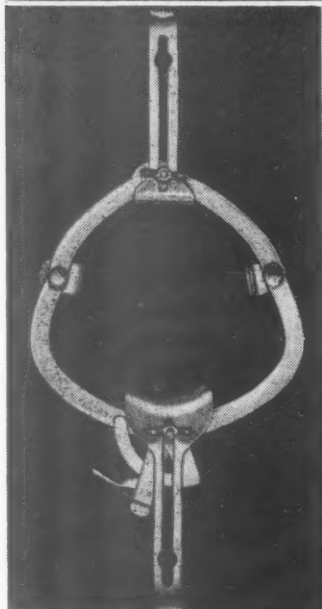
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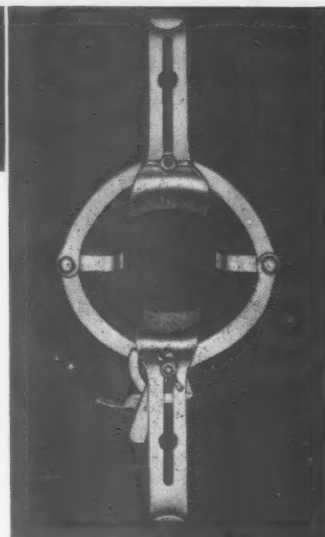
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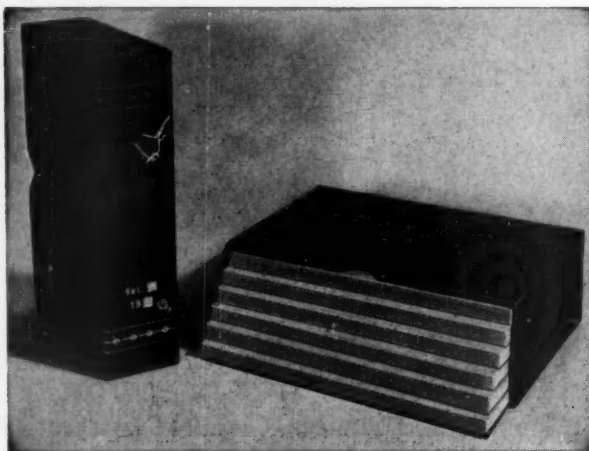
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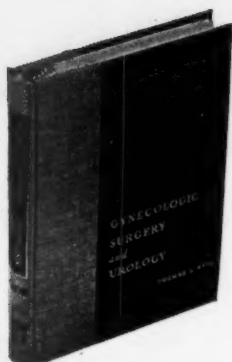
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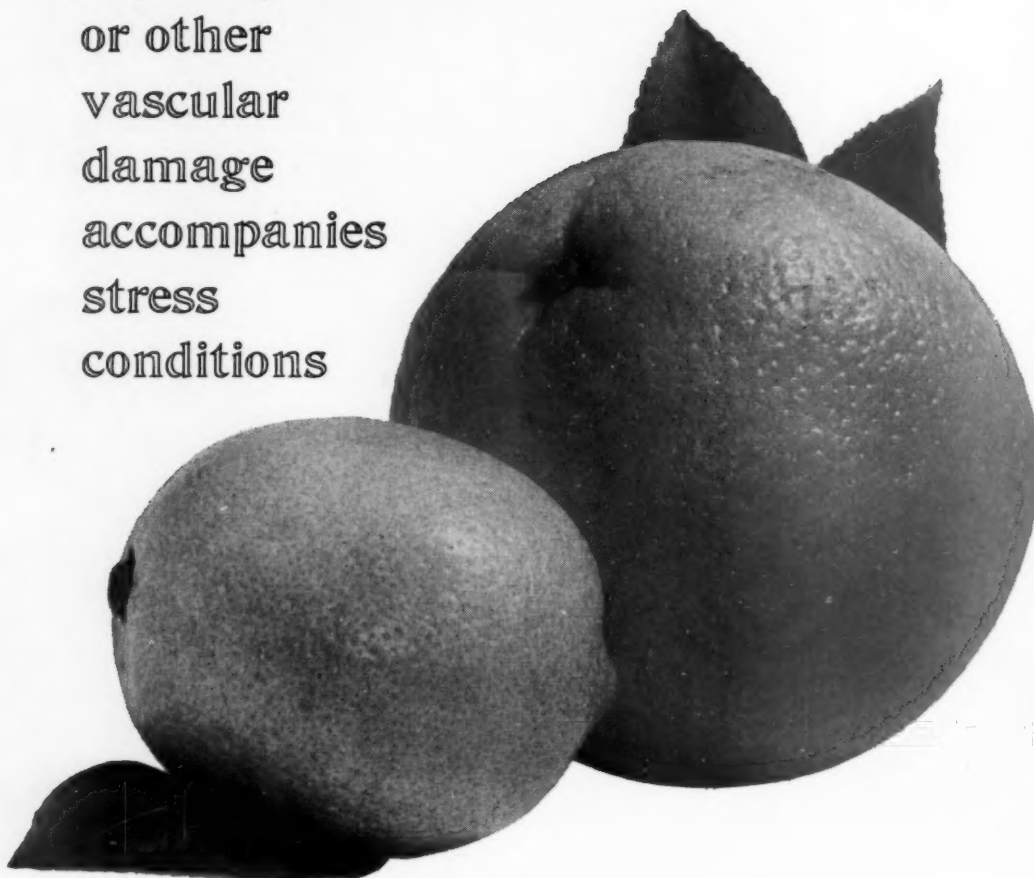
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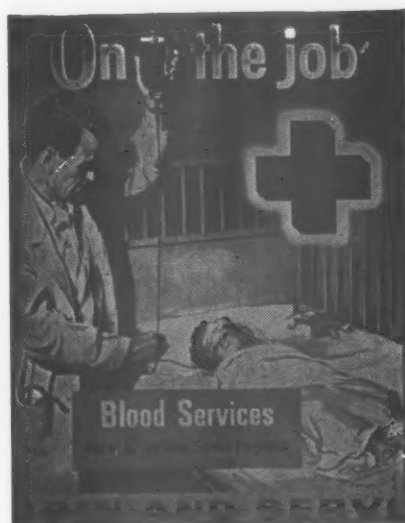
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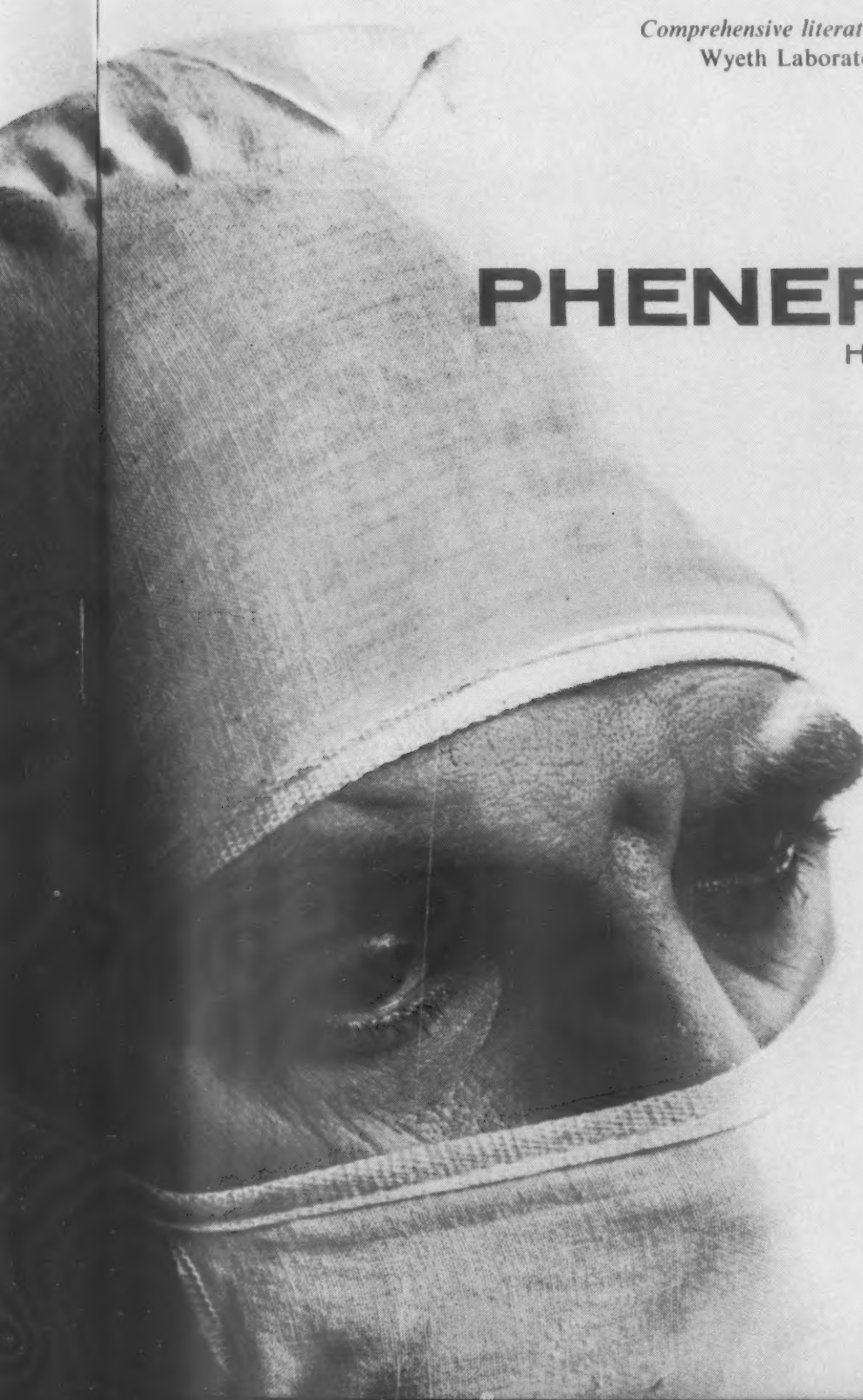
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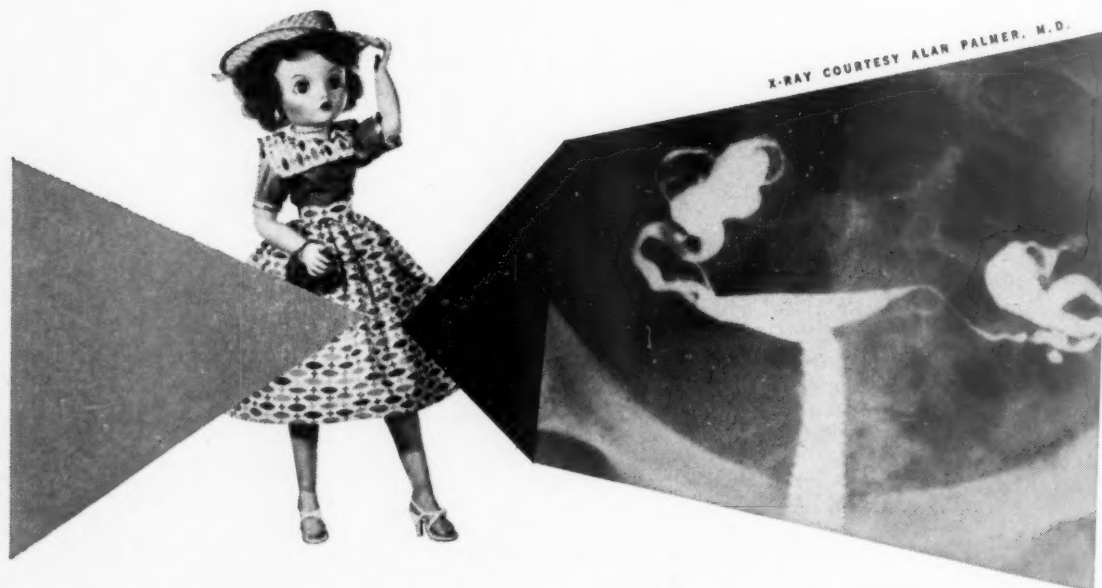
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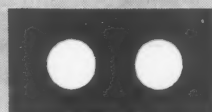
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Rauwiloid[®] + Hexamethonium
alseroxylon 1 mg. and hexamethonium
chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.



Northridge, California

SEP 2 9 1961
MAR 28 1961
OCT 3 1961

ANOTHER STUDY¹ CONFIRMS: EXCELLENT OBSTETRIC ANALGESIA WITH LERITINE

Clinical results with LERITINE in 155 obstetric patients.

■ **rapid relief of pain:** "onset of action is rapid," with "almost immediate analgesia and sedation" and "an analgesic potency 2½ times that of meperidine . . ."

■ **wide margin of safety:** "respiratory depression or alteration in blood pressure was not observed . . . nausea and vomiting during labor were extremely rare . . ."

■ **minimal effect on newborns:** "condition of the infant at the time of delivery . . . when compared with a group sedated with meperidine . . . shows a consistently higher rating."

■ **high patient acceptance:** "We were able to obtain good to excellent amnesia in 64-66% of mothers and subjective satisfaction with the method in 83-85% of cases."

1. Wizenberg, M. J., et al.: Am. J. Obst. & Gynec. 78: 405 (Aug.) 1959.

Leritine
(anileridine)
effective even for
intense pain
parenterally or orally



Additional literature on LERITINE is available to physicians on request.

WARNING: LERITINE may be habit-forming. Subject to Federal Narcotic Law.

*LERITINE is a trademark of Merck & Co., Inc.



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